(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 869 126 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
31.07.2002 Bulletin 2002/31

(51) Int Cl.7: C07D 339/04, C07D 409/12, C07D 409/06, C07D 417/12, A61K 31/385

(21) Application number: 98302532.1

(22) Date of filing: 01.04.1998

(54) Dithiolan derivatives, their preparation and their therapeutic effect

Dithiolan Derivate, deren Herstellung und deren Heileffekt

Dérivés de dithiolane leur préparation et leur effet thérapeutique

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: 02.04.1997 JP 8374997
20.01.1998 JP 883798

(43) Date of publication of application:
07.10.1998 Bulletin 1998/41

(60) Divisional application:
00122586.1 / 1 070 710

(73) Proprietor: Sankyo Company Limited
Chuo-ku, Tokyo 103-8426 (JP)

(72) Inventors:
- Fujita, Takashi
Shinagawa-ku, Tokyo (JP)
- Yokoyama, Tomihisa
Shinagawa-ku, Tokyo (JP)

(74) Representative: Gibson, Christian John Robert
MARKS & CLERK,
57/60 Lincoln's Inn Fields
London WC2A 3LS (GB)

(56) References cited:
WO-A-97/21444
DE-A- 4 327 462
DE-B- 1 210 892
DE-B- 1 210 893
FR-A- 1 294 134
FR-A- 2 707 983
GB-A- 2 148 296

- CHEMICAL ABSTRACTS, vol. 106, no. 74, 1987 Columbus, Ohio, US; abstract no. 129241r, page 633; column 2; XP002072988 & JP 61 170 733 A (FUJI PHOTO)
- R.SZAJEWSKI ET AL.: "RATE CONSTANTS A.EQUILIBRIUM CONSTANTS FOR THIOL-DISULFIDE INTERCHANGE REACTIONS INVOLVING OXIDIZED GLUTATHIONE." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 102, no. 6, 1980, pages 2011-2026, XP002072983 DC US
- J.BUSTAMANTE ET AL.: "ANTIOXIDANT INHIBITION OF THYMOCYTE APOPTOSIS BY DIHYDROLIPOIC ACID." FREE RADICAL BIOL. MED., vol. 19, no. 3, 1995, pages 339-347, XP002072984 USA
- G.BIEWENGA ET AL.: "LIPOIC ACID FAVORS THIOLSULFINATE FORMATION" ARCH. BIOCHEM. BIOPHYS., vol. 312, no. 1, 1994, pages 114-120, XP002072985 SAN DIEGO
- CHANDAN K. SEN: "REGULATION OF CELLULAR THIOLS IN HUMAN LYMPHOCYTES BY ALFA-LIPIOC ACID" FREE RADICAL BIOL. MED., vol. 22, no. 7, 1997, pages 1241-1257, XP002072986 USA
- REGINA KLIUKIENE ET AL.: "THE PROTECTIVE EFFECTS OF DIHYDROLIPOAMIDE A.GLUTATHIONE AGAINST PHOTODYNAMIC DAMAGE BY A1-PHTALOCYANINE TETRASULFONATE." BIOCHEM.MOL.BIOL.INT., vol. 41, no. 4, April 1997, pages 707-713, XP002072987 SYDNEY,SAN DIEGO,...

EP 0 869 126 B1

Description

[0001] The present invention relates to a series of new dithiolan derivatives having an excellent ability to enhance the activity of glutathione reductase. The invention also provides a process for preparing these compounds and methods and compositions using them.

[0002] Glutathione is found throughout the tissues of the living body, is a major reducing agent in cells, and plays a very important role in the oxidation-reduction metabolic processes. In particular, reduced glutathione (GSH), thanks to the presence of a thiol group, plays a key role in various cellular defence and repair mechanisms. Glutathione peroxidase catalyses the reactions involved in these mechanisms, and is an important enzyme in the antioxidant system, in which peroxides (e.g. hydrogen peroxide, lipid peroxides and so on) are reduced by GSH. On the other hand, glutathione reductase is an enzyme which reduces oxidized glutathione (oxidized-type glutathione: GSSG) in the presence of NADPH to regenerate GSH.

[0003] The antioxidant system comprising these materials and enzymes protects cells from the harmful effects of oxidising materials (e.g. above described peroxides, free radicals and so on). Oxidative stress occurs when the balance between oxidising materials and the antioxidant mechanisms is shifted in favour of the former [J. Appl. Physiol. 1996 Nov., 81(5), 2199-2202]. It has been reported that oxidative stress is associated with various diseases, such as coronary heart disease, cataracts, pulmonary diseases (e.g., idiopathic pulmonary fibrosis, adult respiratory distress syndrome, emphysema, asthma, bronchopulmonary dysplasia and interstitial pulmonary fibrosis), chronic renal failure, disorders of the nervous system including the peripheral nervous system and the central nervous system (e.g., Parkinson's disease, schizophrenia, Alzheimer's disease, epilepsy, amyotrophic lateral sclerosis and cerebral ischaemia), gastric ulcers, diabetes, hepatocyte necrosis and apoptosis including ethanol-induced hepatopathy, viral diseases (including influenza, hepatitis B and HIV), and colorectal cancer [J. Appl. Physiol. 1996 Nov., 81(5), 2199-2202; Free Radical Biology & Medicine, Vol. 21 No. 6, 845-853 (1996); Free Radical Biology & Medicine, Vol. 20 No. 7, 925-931 (1996); Gastroenterology, 112, 855-863 (1997); Free Radical Biology & Medicine, Vol. 34, 161-165 (1996); Lancet, 338, 215-216 (1991); Diabetologia, 39, 357-363 (1996); Eur. J. Cancer., 1996 Jan, 32A(1), 30-38; Am. J. Med., 1991 Sep 30. 91(3c), 95s-105s; Alcohol. Clin. Exp. Res., 1996 Dec. 20(9 Suppl), 340A-346A; Free Radical Biology & Medicine, Vol. 21 No. 5, 641-649 (1996); Pharmacol. Toxicol., 1997 Apr, 80(4), 159-166; Cell. Mol. Biol. (Noisy-le-grand) 1996 Feb, 42(1), 17-26; Prostaglandins. Leukot. Essent. Fatty Acids, 1996 Aug, 55(1-2), 33-43; FASEB J., 1995 Sep, 9(12), 1173-1182].

[0004] In addition to the above, oxidative stress is thought to be a factor in Down's syndrome, nephritis, pancreatitis, dermatitis, fatigue, rheumatism, various malformations (e.g. Duchenne muscular dystrophy, Becker dystrophy, Dubin-Johnson-Spring syndrome, favism and so on), Fanconi's anemia, canceration and metastases, septicemia, enhanced permeability of the blood vessels, leukocyte adherence, retinopathy of prematurity, siderosis, toxic effects of medicines (e.g. carcinostatics including platinum chelate, antibiotics, antiparasitics, paraquat, carbon tetrachloride and halothane) and radiogenic damages [Yoshihiko Oyanagi, Superoxide dismutase and agents controlling active oxygen species].

[0005] In WO94/12527, it is disclosed that compounds which enhance the synthesis of endogenous GSH are suitable for human therapy, in particular for the treatment of various diseases induced by glutathione deficiency, such as the pathological states related to oxidative tissue damage, in particular when resulting from an excess of free radicals. Some examples of such diseases are: intracellular oxidative state disequilibrium following alcohol abuse, exposure to xenobiotic agents, damage caused by radiation, hepatic diseases, intoxication from drugs and chemical agents, poisoning by heavy metals, physiological brain ageing (e.g. Parkinson's disease), brain degeneration due to decreased glutathione levels caused by altered antioxidant defence mechanisms, such as acute and chronic neurodegenerative diseases (e.g., acute pathologies such as: acute ischaemic states, in particular cerebral ictus, hypoglycaemia, and epileptic attacks; chronic pathologies such as: amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's chorea), diseases related to altered functionality of the immune system, in particular resulting from tumour immunotherapy, and infertility, in particular male infertility. It is also disclosed that the compounds are suitable for organ reperfusion following ischaemic events mainly imputable to free radicals.

[0006] Furthermore, in Japanese patent publication Kokai Showa 64-26516, it is disclosed that a compound which increases glutathione levels is useful for the treatment and prevention of various diseases including cataracts, hepatic disorders, nephritic disorders.

[0007] At this time, lipoic acid (thioctic acid), which has dithiolan ring in its molecule, is known to influence the biosynthesis and regeneration of reduced glutathione [I. Maitra et al., Free Radical Biology & Medicine, Vol. 18 No. 4, 823-829 (1995)]. In this literature, it is reported that the total glutathione (oxidized and reduced glutathione) level is decreased by administering buthionine sulphoximine (BSO), which is an inhibitor of glutathione synthetase, to newborn rats, that the decrease is prevented by administering lipoic acid together with BSO, and that cataract formation is suppressed. In addition, the literature describes a test on the effects on glutathione reductase achieved by administering only BSO or by administering both BSO and lipoic acid. Considering these results, it is understood that the activity of glutathione reductase does not change when BSO is simply administered by itself, and that the activity of glutathione

reductase also does not increase when lipoic acid is administered in addition to BSO. Bustamente et al., Free Radical Biol.Med., vol.19, no.3, 1995, pages 339-347 and Sen et al., Biochem. Biophys., vol. 312, no.1, 1994, pages 114-120 disclose that lipoamide stimulates the production of reduced glutathione (GSH). Szajewski et al., J.Am.Chem.Soc., vol. 102, no.6, pages 2011-2026 discloses the use of lipoamide in a study of thiol-disulfide interchange reactions involving oxidised glutathione.

[0008] It can, therefore, be deduced from this literature that the total glutathione level will be increased and that disorders can be treated when lipoic acid is administered to a patient who is suffering from a disease caused by a deficiency of glutathione synthesis, but lipoic acid is not thought to provide sufficient effect against diseases which occur in spite of enough glutathione synthesis since it is understood not to increase glutathione reductase activity.

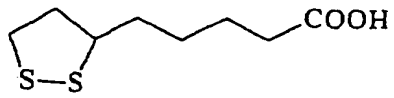
[0009] On the contrary, if the activity of glutathione reductase can be increased, then whether glutathione synthesis is or is not adequate, diseases which occur in spite of enough glutathione synthesis and which are caused by oxidative stress can be prevented or treated since the supply of reduced glutathione is increased.

[0010] Furthermore, in general, in the case of ophthalmologic diseases, such as cataracts, topical application to the eyes is preferred to oral administration. However, since lipoic acid is a powerful stimulant, it is impossible to administer it to the eyes.

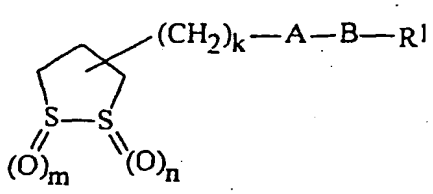
[0011] Compounds having pharmacological activity which contain the dithiolan ring present in the compounds of the present invention are disclosed in FR-A-2,707,983; FR-A-1,294,134; DE-B-1,210,892; GB-A-2,148,296; Biewenga et al., Arch.Biochem. Biophys., vol.312, no.1, 1994, pages 114-120; and Kliukiene et al., Biochem. Mol. Biol.Int., vol.41, no.4, April 1997, pages 707 to 713. Other compounds containing a dithiolan ring are disclosed in DE-B-1,210,893 and Chem.Abs., vol.106, no.74, 1987 Columbus, Ohio, US, abstract no.129241r. None of these documents discloses compounds of the present invention nor do they suggest that the compounds of the present invention would have ability to enhance the activity of glutathione reductase.

[0012] We have now discovered a series of dithiolan derivatives, which have the ability to cause a significant increase in the activity of glutathione reductase and which also remove peroxides. Moreover, the compounds of the present invention are less stimulating to the eyes than lipoic acid and similar known compounds are thus especially suitable for topical application.

[0013] For the avoidance of doubt, the compounds of the present invention are named following the IUPAC Rules, using, as appropriate, lipoic acid (also known as thioctic acid) as the parent compound. This compound has the formula:



[0014] The compounds of the present invention are those compounds of formula (I):



(I)

in which:

one of m and n represents 0, and the other represents 0, 1 or 2;

k represents 0 or an integer of from 1 to 12;

A represents a group of formula $-CON(R^2)SO_2-$, in which R^2 represents

a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms, an aralkyl group defined below the aryl moiety of which may optionally be substituted by from 1 to 3 of substituents β defined below, an acyl group defined below,

or one of substituents α defined below;

B represents a single bond, or a group of formula -N(R^5)- or -N(R^6)N(R^5)-

in which R^5 and R^6 are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms, an aralkyl group defined below the aryl moiety of which may optionally be substituted by from 1 to 3 of substituents β defined below, an acyl group defined below, or one of substituents α defined below,
or R^5, together with R^1 and the nitrogen atom to which they are bonded, may form a heterocyclic ring having from 5 to 7 ring atoms defined below;

R^1 represents:

a hydrogen atom,
one of substituents α, defined below, or
an alkyl group having from 1 to 12 carbon atoms which is unsubstituted or is substituted by from 1 to 3 of substituents α defined below and/or substituents γ defined below or such a substituted or unsubstituted alkyl group in which the carbon chain is interrupted by an oxygen atom and/or a sulfur atom,

or, where B represents a single bond or a group of formula -N(R^5)- [in which R^5 is as defined above], R^1 may represent a hydroxy group or a group of formula -OR^7 (in which R^7 represents a lower alkyl group defined below, a lower alkenyl group defined below, an aralkyl group defined below of which the aryl moiety may optionally be substituted by from 1 to 3 of substituents β defined below, or one of substituents α);

Substituents α are selected from aryl groups defined below, heterocyclic groups defined below, aryl groups defined below substituted with from 1 to 3 of substituents β, and heterocyclic groups defined below substituted with from 1 to 3 of substituents β;

Substituents β are selected from lower alkyl groups defined below, halogenated lower alkyl groups defined below, lower alkoxy groups defined below, lower alkylthio groups defined below, hydroxy groups, carboxy groups, optionally-substituted carbamoyl groups defined below, lower alkoxycarbonyl groups defined below, halogen atoms, nitro groups, amine residues defined below, sulfo groups, sulfamoyl groups. cyano groups, and hydroxy-substituted lower alkyl groups defined below:

Substituents γ are selected from lower alkoxy groups defined below, lower alkylthio groups defined below, hydroxy groups, nitrooxy groups, carboxy groups, lower alkoxycarbonyl groups defined below, halogen atoms, sulfo groups. sulfamoyl groups, amine residues defined below, and optionally-substituted carbamoyl groups defined below;

and pharmaceutically acceptable salts thereof;

the aryl groups referred to in the definition of substituents α are carbocyclic aromatic hydrocarbons having from 6 to 14 ring carbon atoms in one or more aromatic carbocyclic rings which may be fused to a cycloalkyl group having from 3 to 10 ring carbon atoms;

the aralkyl groups referred to in the definitions of R^2, R^5, R^6 and R^7 are alkyl groups having from 1 to 6 carbon atoms which are substituted by from 1 to 3 aryl groups defined above;

the acyl groups referred to in the definitions of R^2, R^5 and R^6 are selected from the group consisting of alkylcarbonyl groups having from 1 to 30 carbon atoms, halogenated alkylcarbonyl groups having from 2 to 6 carbon atoms, alkoxyalkylcarbonyl groups in which each of the alkoxy and alkyl moieties has from 1 to 4 carbon atoms, unsaturated alkylcarbonyl groups having from 3 to 6 carbon atoms, arylcarbonyl groups in which the aryl moiety is as defined above, halogenated arylcarbonyl groups in which the aryl moiety is as defined above, (C_{1-6}) alkyl-substituted arylcarbonyl groups in which the aryl moiety is as defined above, hydroxy-substituted arylcarbonyl groups in which the aryl moiety is as defined above, (C_{1-6}) alkoxy-substituted arylcarbonyl groups in which the aryl moiety is as defined above, nitro-substituted arylcarbonyl groups in which the aryl moiety is as defined above, lower alkoxycarbonyl-substituted arylcarbonyl groups in which the aryl moiety is as defined above and the alkoxycarbonyl substituents have from 2 to 7 carbon atoms, aryl-substituted arylcarbonyl groups in which each aryl moiety is as defined above, alkoxycarbonyl groups having from 2 to 7 carbon atoms, alkoxycarbonyl groups having from 2 to

7 carbon atoms in which the alkoxy moiety is substituted with a halogen atom or a tri-(C_{1-6}) alkyl silyl group, aralkylcarbonyl groups in which the alkyl moiety has from 1 to 6 carbon atoms and the aryl moiety is as defined above and may optionally be substituted by 1 or 2 alkoxy groups having from 1 to 6 carbon atoms or nitro groups, lower alkanesulphonyl groups in which the lower alkyl moiety has from 1 to 6 carbon atoms, halogenated lower alkanesulphonyl groups in which the lower alkyl moiety has from 1 to 6 carbon atoms and arylsulphonyl groups in which the aryl moiety is as defined above;

the 5- to 7-membered heterocyclic rings which may be formed from a combination of R^1, R^5 and the nitrogen atom to which they are attached have from 1 to 3 sulphur and/or oxygen and/or nitrogen atoms of which at least one must be a nitrogen atom, said groups being optionally substituted by 1 or 2 oxygen atoms and/or 1 to 3 of substituents β defined above, and further optionally being fused with a carbocyclic or heterocyclic group having from 3 to 6 ring atoms;

the lower alkyl groups referred to in the definitions of R^7 and substituents β are straight or branched chain groups having from 1 to 6 carbon atoms;

the lower alkenyl groups referred to in the definition of R^7 are straight or branched chain groups having from 2 to 6 carbon atoms;

the heterocyclic groups referred to in the definition of substituents α have from 5 to 7 ring atoms of which from 1 to 3 are sulphur and/or oxygen and/or nitrogen atoms, said groups being saturated or unsaturated, optionally being substituted by 1 or 2 oxygen and/or sulphur atoms, and further optionally being fused with a carbocyclic or heterocyclic group having from 3 to 6 ring atoms;

the halogenated lower alkyl groups referred to in the definition of substituents β comprise a lower alkyl group as defined above which is substitituted by 1 or more halogen atoms;

the lower alkoxy groups referred to in the definitions of substituents β and substituents γ are

straight or branched chain groups having from 1 to 6 carbon atoms;

the lower alkylthio groups referred to in the definitions of substituents β and substituents γ are

straight or branched chain groups having from 1 to 6 carbon atoms;

the amine residues referred to in the definitions of substituents β and substituents γ are groups of formula $-NR^aR^b$ wherein R^a and R^b are the same or different and each represents a hydrogen atom, a lower alkyl group as defined above, a cycloalkyl group having from 3 to 8 ring carbon atoms, an aryl group as defined above, a heterocyclic group as defined above, or R^a and R^b together with the nitrogen atom to which they are attached represent a 5- to 7-membered nitrogen-containing heterocyclic group as defined above;

the optionally-substituted carbamoyl groups referred to in the defintions of substituents β and substituents γ are groups of formula $-CONR^{a'}R^{b'}$ wherein $R^{a'}$ and $R^{b'}$ are the same or different and each represents any of the atoms or groups represented by R^a and R^b defined above or one of $R^{a'}$ and $R^{b'}$ represents a hydrogen atom and the other represents an acyl group as defined above or an aminosulphonyl group;

the lower alkoxycarbonyl groups referred to in the definitions of substituents β and substituents γ comprise a carbonyl group which is substituted by a straight or branched chain alkoxy group having from 1 to 6 carbon atoms; and

the hydroxy-substituted lower alkyl groups referred to in the definitions of substituents β and substituents γ are lower alkyl groups as defined above which are substituted by 1 or more hydroxy groups.

[0015] The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for enhancing the activity of glutathione reductase in a mammal, which may be human.

[0016] The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of cataract in a mammal, which may be human.

[0017] In the compounds of the present invention, one of m and n represents 0, and the other represents 0, 1 or 2. Preferably, either both of m and n represent 0, or one of m and n represents 0 and the other represents 1. More preferably, both of m and n represent 0.

[0018] We prefer those compounds of formula (I) in which k represents 0 or an integer of from 1 to 6, more preferably an integer of from 2 to 6, and most preferably an integer of from 4 to 6.

[0019] Where R^1 or substituent α represents an aryl group; this is a carbocyclic aromatic hydrocarbon group having from 6 to 14 ring carbon atoms in one or more aromatic carbocyclic rings or is such a group which is fused to a cycloalkyl group having from 3 to 10 ring carbon atoms. Examples of carbocyclic aromatic hydrocarbon groups having from 6 to 14 ring carbon atoms in one or more aromatic carbocyclic rings include the phenyl, naphthyl (1- or 2- naphthyl), phenanthrenyl and anthracenyl groups. An example of a group in which an aromatic carbocyclic ring is fused to a cycloalkyl group is the 2-indanyl group.

[0020] Where R^1 or substituent a represents a heterocyclic group, this has from 5 to 7 ring atoms of which from 1 to 3 are sulphur and/or oxygen and/or nitrogen hetero-atoms. The group may be saturated or it may be unsaturated and preferably aromatic.

[0021] Where the heterocyclic groups referred to herein have 3 hetero-atoms, we prefer that all three, two or one of these atoms are nitrogen atoms, and, correspondingly, none, one or two are sulphur and/or oxygen atoms.

[0022] Examples of such saturated heterocyclic groups include, for example, the pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dithiolanyl, thiadiazolidinyl, oxadiazolidinyl, dithiazolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl dioxanyl and homopiperazinyl groups. Of these groups, we particularly prefer those 5- to 7-membered saturated heterocyclic groups which have one or two nitrogen atoms or have one nitrogen atom and one sulphur atom or one oxygen atom, such as the pyrrolidinyl, thiazolidinyl, imidazolidinyl, piperidyl, morpholinyl, thiomorpholinyl and piperazinyl groups.

[0023] If desired, the above-described saturated heterocyclic groups may be substituted by one or two sulphur and/or oxygen atoms to form an oxo group and/or a thioxo group. Examples of such groups include the piperidonyl, pyrrolidonyl, thiazolidonyl, dioxothiazolidinyl, thioxodithiazolidinyl, dioxoimidazolidinyl and dioxooxazolidinyl groups.

[0024] Also, if desired, the above-described saturated heterocyclic group may be fused with another cyclic group, preferably having 3, 4, 5 or 6 ring atoms, and which may be carbocyclic or heterocyclic, most preferably a benzene ring. Examples of such fused ring groups include the benzodioxanyl, indolinyl, isoindolinyl, benzooxazinyl, benzothiazolidinyl, benzothiazinyl, chromanyl, 6-acetoxy-2.5,7,8-tetramethylchroman-2-yl, and isoindol-1,3-dion-2-yl groups.

[0025] Examples of such aromatic heterocyclic groups include the furyl, thienyl, pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl groups. Of these, those 5- to 7-membered aromatic heterocyclic groups which have at least one nitrogen atom and may have an oxygen atom and/or a sulphur atom are preferred. Examples of such groups include the pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl groups. The pyridyl, imidazolyl, oxazolyl, pyrazinyl and thiazolyl groups are most preferred.

[0026] Also, if desired, the above-described aromatic heterocyclic group may be fused with another cyclic group, preferably having 3, 4, 5 or 6 ring atoms, and which may be carbocyclic or heterocyclic, most preferably a benzene ring. Examples of such fused ring groups include the indolyl, benzofuryl, benzothienyl, benzooxazolyl, benzoimidazolyl, quinolyl, isoquinolyl, quinoxalyl groups.

[0027] Also, the above-described aromatic heterocyclic groups may be substituted by one or two sulphur and/or oxygen atoms to form an oxo group and/or a thioxo group, and examples of such groups include the pyridonyl, oxazolonyl, pyrazolonyl, isoxazolonyl and thioxodithiazolyl groups.

[0028] If desired, any of the above aryl and heterocyclic groups may be substituted by one or more, preferably from 1 to 3, of substituents β, defined above and exemplified below.

[0029] Where R^1 represents an alkyl group having from 1 to 12 carbon atoms, this may be a straight or branched chain group which may be unsubstituted or may be substituted by from 1 to 3 of substituents γ, defined above and exemplified below. Examples of such unsubstituted alkyl groups include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 2-hexyl, 3-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 3,3-dimethylpentyl, octyl, 2-methylheptyl, 2-ethylhexyl, 1,1,3,3-tetramethylbutyl, nonyl, 2-nonyl, 3-nonyl, 4-nonyl, 5-nonyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 8-methyloctyl, 6,6-dimethylheptyl, decyl, 2-decyl, 3-decyl, 4-decyl, 5-decyl, 2-methylnonyl, 3-methylnonyl, 4-methylnonyl, 6,6-dimethyloctyl, undecyl, 2-undecyl, 3-undecyl, 4-undecyl, 5-undecyl, 6-undecyl, 2-methyldecyl, 3-methyldecyl, 4-methyldecyl, 5-methyldecyl, 6-methyldecyl, 7-methyldecyl, 8-methyldecyl, 9-methyldecyl, 7-ethylnonyl, dodecyl, 2-dodecyl, 3-dodecyl, 4-dodecyl, 5-dodecyl, 6-dodecyl, 2-methylundecyl, 3-methylundecyl, 4-methylundecyl, 5-methylundecyl, 6-methylundecyl, 7-methylundecyl, 8-methylundecyl, 9-methyl-

undecyl and 10-methylundecyl groups. Of these, straight or branched alkyl groups having from 1 to 6 carbon atoms are preferred, straight or branched alkyl groups having from 1 to 4 carbon atoms are more preferred, and the methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups are most preferred.

[0030] Alternatively, R^1 may represent such an alkyl group in which the carbon chain is interrupted by one or more oxygen atoms and/or sulphur atoms. Examples of such groups include any of the above alkyl groups which are substituted by a single alkoxy or alkylthio group, which itself may be further substituted by an alkoxy or alkylthio group, the alkoxy and alkylthio groups being as exemplified below in relation to substituents β and γ. Specific examples of such groups include alkoxyalkyl groups having from 2 to 10 carbon atoms, alkylthioalkyl groups having from 2 to 10 carbon atoms, benzyloxyalkyl groups of which the alkyl part has from 1 to 5 carbon atoms and benzylthioalkyl groups of which the alkyl part has from 1 to 5 carbon atoms (the benzyl part of the benzyloxyalkyl and benzylthioalkyl groups may be unsubstituted or substituted with from 1 to 3 of substituents β) groups. Of these, the methoxymethyl, methoxyethyl, ethoxymethyl. methylthiomethyl, methylthioethyl, ethylthiomethyl, benzyloxymethyl, benzyloxyethyl, benzylthiomethyl and 4-methoxybenzylthiomethyl groups are preferred.

[0031] Where R^2, R^5 or R^6 represents an alkyl group having from I to 12 carbon atoms, this may be a straight or branched chain group, as defined and exemplified above in relation to R^1.

[0032] Where R^2, R^5 or R^6 represents an aralkyl group, this is a lower alkyl group (preferably having from 1 to 6 carbon atoms, more preferably from 1 to 4 carbon atoms, still more preferably from 1 to 3 carbon atoms and most preferably 1 or 2 carbon atoms) which is substituted by from 1 to 3 aryl groups as defined and exemplified above in relation to R^1. Specific examples of such aralkyl groups include the benzyl, 1-phenylethyl, 2-phenylethyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl and 9-anthrylmethyl groups. Of these, the benzyl, 1-phenylethyl and 2-phenylethyl groups are preferred. Any of the above groups may be unsubstituted or it may be substituted by from 1 to 3 of substituents γ defined and exemplified below.

[0033] Where R^2, R^5 or R^6 represents an acyl group, this may be an aliphatic, aromatic or heterocyclic acyl group, for example:

an alkylcarbonyl group having from 1 to 30, preferably from 1 to 21 and more preferably from 1 to 8 carbon atoms, such as the formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, isovaleryl, octanoyl, nonylcarbonyl, decylcarbonyl, 3-methylnonylcarbonyl, 8-methylnonylcarbonyl, 3-ethyloctylcarbonyl, 3,7-dimethyloctylcarbonyl, undecylcarbonyl, dodecylcarbonyl, tridecylcarbonyl, tetradecylcarbonyl, pentadecylcarbonyl, hexadecylcarbonyl, 1-methylpentadecylcarbonyl, 14-methylpentadecylcarbonyl, 13,13-dimethyltetradecylcarbonyl, heptadecylcarbonyl, 15-methylhexadecylcarbonyl, octadecylcarbonyl, 1-methylheptadecylcarbonyl, nonadecylcarbonyl, eicosylcarbonyl and heneicosylcarbonyl groups; of these, the groups having from 1 to 5 carbon atoms are most preferred;

a halogenated alkylcarbonyl group having from 2 to 6 carbon atoms, preferably 2 or 3 carbon atoms, such as the chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl groups;

a lower alkoxyalkylcarbonyl group in which the alkyl and alkoxy parts each preferably has from 1 to 4 carbon atoms, such as the methoxyacetyl group;

an unsaturated alkylcarbonyl group having from 3 to 6 carbon atoms, such as the acryloyl, propioloyl, methacryloyl, crotonoyl, allylcarbonyl, isocrotonoyl and (E)-2-methyl-2-butenoyl groups;

an arylcarbonyl group, such as the benzoyl, α-naphthoyl and β-naphthoyl groups;

a halogenated arylcarbonyl group, such as the 2-bromobenzoyl and 4-chlorobenzoyl groups;

a lower alkyl-substituted arylcarbonyl group, such as the 2,4,6-trimethylbenzoyl and 4-toluoyl groups;

a hydroxy-substituted arylcarbonyl group, such as the 3,5-dimethyl-4-hydroxybenzoyl and 3,5-di-t-butyl-4-hydroxybenzoyl groups;

a lower alkoxy-substituted arylcarbonyl group, such as the 4-anisoyl group;

a nitro-substituted arylcarbonyl group such as the 4-nitrobenzoyl and 2-nitrobenzoyl groups;

a lower alkoxycarbonyl-substituted arylcarbonyl group, such as the 2-(methoxycarbonyl)benzoyl group;

an aryl-substituted arylcarbonyl group, such as the 4-phenylbenzoyl group;

a lower alkoxycarbonyl group preferably having from 2 to 7 carbon atoms, such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl and isobutoxycarbonyl groups;

a lower alkoxycarbonyl group, preferably having from 2 to 7 carbon atoms, which is substituted with a halogen atom or a tri-lower alkylsilyl group, such as the 2,2,2-trichloroethoxycarbonyl and 2-trimethylsilylethoxycarbonyl groups;

an aralkylcarbonyl group, of which the aryl ring may be unsubstituted or may be substituted with 1 or 2 lower alkoxy or nitro groups, such as the benzylcarbonyl, 4-methoxybenzylcarbonyl, 3,4-dimethoxybenzylcarbonyl, 2-nitrobenzylcarbonyl and 4-nitrobenzylcarbonyl groups;

a lower alkanesulphonyl group, preferably having from 1 to 6 carbon atoms, such as the methanesulphonyl, ethanesulphonyl and propanesulphonyl groups;

a halogenated lower alkanesulphonyl group, preferably having from 1 to 6 carbon atoms, such as the chloromethanesulphonyl, trifluoromethanesulphonyl and pentafluoroethanesulphonyl groups; and

an arylsulphonyl group, in which the aryl part is as defined and exemplified above in relation to R^1, such as the benzenesulphonyl and p-toluenesulphonyl group.

[0034] Of the above groups, we prefer the aliphatic acyl groups, the aromatic acyl groups, the alkoxycarbonyl groups and the lower alkanesulphonyl groups, more preferably the alkylcarbonyl groups and the lower alkoxycarbonyl groups.

[0035] Where R^5, together with R^1 and the nitrogen atom to which they are attached forms a heterocyclic group, this has from 5 to 7, more preferably 5 or 6, ring atoms of which from 1 to 3 are sulphur and/or oxygen and/or nitrogen hetero-atoms, at least one being a nitrogen atom. Preferably there are one or two nitrogen atoms and none or one oxygen atom or sulphur atom. Examples of such groups include the pyrrolidino, 3-thiazolidinyl, piperidino, piperazino, morpholino, thiomorpholino, homopiperazino, imidazolidinyl and imidazolyl groups. Such groups may be substituted or unsubstituted, preferably with one or two oxygen atoms and/or with 1 to 3 of substituents β, as defined above, and may be fused with another cyclic group, preferably having 3, 4, 5 or 6 ring atoms, and which may be carbocyclic or heterocyclic, most preferably a benzene ring. Examples of such groups are the N-methylpiperazino, N-t-butoxycarbonylpiperazino, 1-indolinyl, 2-carboxy-1-indolinyl, 2-methoxycarbonyl-1-indolinyl, 3,4-dimethyl-indolin-2,5-dione-1-yl and isoindol-1,3-dion-2-yl groups.

[0036] Where R^7 or substituent β represents a lower alkyl group, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, hexyl, isohexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl and 2-ethylbutyl groups. Of these, we prefer those alkyl groups having from 1 to 4 carbon atoms, particularly the methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups, and most preferably the methyl group.

[0037] Where R^7 represents a lower alkenyl group, this may be a straight or branched chain group having from 2 to 6, preferably 3 or 4, carbon atoms, and examples include the vinyl, allyl, methallyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl and 4-hexenyl groups, of which the vinyl, allyl, methallyl, 1-propenyl, isopropenyl and butenyl groups are preferred, the allyl and 2-butenyl groups being most preferred.

[0038] Where R^7 represents an aralkyl group, this may be any of the aralkyl groups defined and exemplified above in relation to R^2.

[0039] Where substituent β represents a halogenated lower alkyl group, this may be any of the above alkyl groups which is substituted by at least one halogen atom. Although there is no critical limitation on the number of halogen substituents, and the group may, if desired, be perhalogenated, in general, from 1 to 3 halogen atoms, selected from fluorine, chlorine, bromine and iodine atoms, are preferred. Examples of such haloalkyl groups include the chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 3-chloropropyl, 3-fluoropropyl, 3-bromopropyl, 3-iodopropyl, 3,3,3-trichloropropyl, 3,3,3-trifluoropropyl, 4-chlorobutyl, 4-fluorobutyl, 4-bromobutyl and 4-iodobutyl groups.

[0040] Where substituent β or substituent γ represents a lower alkoxy group, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, isopentyloxy, neopentyloxy, 2-methylbutoxy, 1-ethylpropoxy, hexyloxy, isohexyloxy, 3-methylpentyloxy, 2-methylpentyloxy, 1-methylpentyloxy, 3,3-dimethylbutoxy, 2,2-dimethylbutoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,3-dimethylbutoxy and 2-ethylbutoxy groups.

Of these, we prefer those alkoxy groups having from 1 to 4 carbon atoms, particularly the methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy groups, and most preferably the methoxy group.

[0041] Where substituent β or substituent γ represents a lower alkylthio group, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, neopentylthio, 2-methylbutylthio, 1-ethylpropylthio, hexylthio, isohexylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 1-methylpentylthio, 3,3-dimethylbutylthio, 2,2-dimethylbutylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,3-dimethylbutylthio and 2-ethylbutylthio groups. Of these, we prefer those alkylthio groups having from 1 to 4 carbon atoms, particularly the methylthio, ethylthio, propylthio, isopropylthio, butylthio and isobutylthio groups, and most preferably the methylthio group.

[0042] Where substituent β or substituent γ represents an amine residue, this is a group of formula $-NR^aR^b$, where R^a and R^b are the same or different and each represents a hydrogen atom, a lower alkyl group (as defined and exemplified above in relation to R^7 or substituent β), a cycloalkyl group having from 3 to 8, preferably 5 or 6, ring carbon atoms, an aryl group (as defined and exemplified above in relation to R^1), an aralkyl group (as defined and exemplified above in relation to R^2), a heterocyclic group (as defined and exemplified above in relation to R^1), or R^a and R^b together with the nitrogen atom to which they are attached represent a nitrogen-containing heterocyclic group (as defined and exemplified above in relation to R^5 and R^1). Examples of such groups include:

the amino group;

alkylamino and dialkylamino groups, such as the methylamino, ethylamino, isopropylamino, butylamino, dimethylamino, diethylamino, diisopropylamino and dibutylamino groups;

cycloalkylamino and dicycloalkylamino groups, such as the cyclopentylamino, cyclohexylamino, dicyclopentylamino and dicyclohexylamino groups;

saturated cyclic amino groups, that is heterocyclic groups having a nitrogen atom in the ring, such as the pyrrolidino, piperidino, piperazino, N-methylpiperazino, morpholino and thiomorpholino groups;

aryl- and aralkylamino groups of which the nitrogen atom may be substituted with a lower alkyl group, such as the anilino, benzylamino, N-methylanilino and N-methylbenzylamino groups; and

a heterocyclic-substituted amino group, in which the nitrogen atom may be substituted with a lower alkyl group, such as the pyridylamino, N-methylpyridylamino and N-ethylpyridylamino groups.

[0043] Of these, we prefer the amino group, mono- and di-alkylamino groups, saturated cyclic amino groups (such as the pyrrolidino, piperidino, piperazino, N-methylpiperazino, morpholino and thiomorpholino groups) and aryl- and aralkylamino groups of which the nitrogen atom may be substituted with a lower alkyl group (such as the anilino, benzylamino, N-methylanilino and N-methylbenzylamino groups).

[0044] Where substituent β or substituent γ represents a carbamoyl group of which the nitrogen atom may be substituted, this is a group of formula $-CONR^{a'}R^{b'}$, where $R^{a'}$ and $R^{b'}$ are the same or different and each represents any of the atoms or groups represented by R^a and R^b or a one of $R^{a'}$ and $R^{b'}$ represents a hydrogen atom and the other represents an acyl group (which may be any of the acyl groups defined and exemplified above in relation to R^2) or an aminosulphonyl group. Examples of such carbamoyl groups include:

the carbamoyl group;

alkylcarbamoyl and dialkylcarbamoyl groups, such as the methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, diisopropylcarbamoyl and dibutylcarbamoyl groups;

cycloalkylcarbamoyl and dicycloalkylcarbamoyl groups, such as the cyclopentylcarbamoyl, cyclohexylcarbamoyl, dicyclopentylcarbamoyl and dicyclohexylcarbamoyl groups;

saturated cyclic aminocarbonyl groups, that is carbonyl groups attached to a heterocyclic group having a nitrogen atom in the ring, such as the pyrrolidinocarbonyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl, morpholinocarbonyl and thiomorpholinocarbonyl groups;

aryl- and aralkylcarbamoyl groups of which the nitrogen atom may be substituted with a lower alkyl group, such

as the phenylcarbamoyl, benzylcarbamoyl, N-methylphenylcarbamoyl and N-methylbenzylcarbamoyl groups;

a heterocyclic-substituted carbamoyl group, in which the nitrogen atom may be substituted with a lower alkyl group, such as the pyridylcarbamoyl, N-methylpyridylcarbamoyl and N-ethylpyridylcarbamoyl groups; and

acylcarbamoyl groups, especially alkanesulphonylaminocarbonyl groups, such as the methanesulphonylaminocarbonyl group and the aminosulphonylaminocarbonyl group.

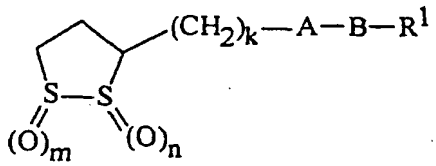
[0045] Of these, we prefer the carbamoyl group, mono- and di-alkylcarbamoyl groups, saturated cyclic carbamoyl groups (such as the pyrrolidinocarbonyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl, morpholinocarbonyl and thiomorpholinocarbonyl groups), aryl- and aralkylcarbamoyl groups of which the nitrogen atom may be substituted with a lower alkyl group (such as the phenylcarbamoyl, benzylcarbamoyl, N-methylphenylcarbamoyl and N-methylbenzylcarbamoyl groups) and alkanesulphonylaminocarbonyl groups (such as the methanesulphonylaminocarbonyl group).

[0046] Where substituent β or substituent γ represents a lower alkoxycarbonyl group, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms in the alkoxy part (i.e. from 2 to 7 carbon atoms in the alkoxycarbonyl part), and examples include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl, 1-ethylpropoxycarbonyl, hexyloxycarbonyl, isohexyloxycarbonyl, 4-methylpentyloxycarbonyl, 3-methylpentyloxycarbonyl, 2-methylpentyloxycarbonyl, 1-methylpentyloxycarbonyl, 3,3-dimethylbutoxycarbonyl, 2,2-dimethylbutoxycarbonyl, 1,1-dimethylbutoxycarbonyl, 1,2-dimethylbutoxycarbonyl, 1,3-dimethylbutoxycarbonyl, 2,3-dimethylbutoxycarbonyl and 2-ethylbutoxycarbonyl groups. Of these, we prefer those alkoxycarbonyl groups having from 1 to 4 carbon atoms, particularly the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl and t-butoxycarbonyl groups, and most preferably the methoxycarbonyl group.

[0047] Where substituent β or substituent γ represents a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom, preferably a fluorine or chlorine atom.

[0048] Where substituent β represents a hydroxy-substituted lower alkyl group, this may be any of the lower alkyl groups defined and exemplified above in relation to R^2 which is substituted by one or more hydroxy groups. Examples of such groups include the hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

[0049] Of the compounds of the present invention, those compounds of formula (I) in which the group of formula $-(CH_2)_k-A-B-R^1$ is bonded to the 3-position of the dithiolan ring are preferred. Such compounds may be represented by the formula (I'):



(I')

(in which A, B, R^1, k, m and n are as defined above).

[0050] Where the compounds of the present invention possess a basic group, such as an amino or imino group, the compounds can form salts with acids. On the other hand, where the compounds of the present invention possess an acidic group, such as a carboxy group or an imido group, they can form salts with bases. There is no particular restriction on the nature of such salts, provided that, where they are intended for pharmaceutical use, they are pharmaceutically acceptable, that is they are not less active (or unacceptably less active) than the compound of formula (I) itself, and are not more toxic (or unacceptably more toxic) than the compound of formula (I) itself.

[0051] Examples of such salts formed between a basic group in the compound of the present invention and an acid include: salts with mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, perchloric acid, carbonic acid, sulphuric acid or phosphoric acid; salts with lower alkylsulphonic acids, such as methanesulphonic acid, trifluoromethanesulphonic acid or ethanesulphonic acid; salts with arylsulphonic acids, such as benzenesulphonic acid or p-toluenesulphonic acid; salts with organic carboxylic acids, such as acetic acid, fumaric acid, tartaric acid, oxalic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid or citric acid; and salts with amino acids, such as glycine, lysine, arginine,

omithine, glutamic acid or aspartic acid.

[0052] Examples of such salts formed between an acidic group in the compound of the present invention and a base include: salts with an alkali metal, such as sodium, potassium or lithium; salts with an alkaline earth metal, such as barium or calcium; salts with another metal, such as magnesium, aluminium or iron; ammonium salts; organic base salts, such as a salt with t-octylamine, dibenzylamine, morpholine, glucosamine, a phenylglycine alkyl ester, ethylenediamine, N-methylglucamine, guanidine, methylamine, dimethylamine, diethylamine, triethylamine, diisopropylamine, cyclohexylamine, dicyclohexylamine, N,N-dibenzylethylenediamine, chloroprocaine, procaine, diethanolamine, N-benzylphenethylamine, piperazine, tetramethylammonium, and tris(hydroxymethyl)aminomethane; and salts with an amino acid, such as glycine, lysine, arginine, ornithine, glutamic acid or aspartic acid.

[0053] Also, when a compound of the present invention is allowed to stand in the air, it may absorb water to form a hydrate. Such hydrates also form a part of the present invention.

[0054] Where a compound of the present invention contains an asymmetric carbon atom in its molecule, it can form optical isomers which are in the R- or S- configuration. Although these are all represented herein by a single molecular formula, the present invention includes both the individual, isolated isomers and mixtures, including racemates thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques.

[0055] Of the compounds of the present invention, we prefer those compounds of formula (I) and salts thereof in which:

(A) one of m and n is 0, and the other is 0 or 1;

(B) k is 0 or an integer of from 1 to 8;

(C) R^1 represents a hydroxy group, an alkoxy group having from 1 to 5 carbon atoms, a heterocyclic group, an alkyl group having from 1 to 12 carbon atoms which is unsubstituted or is substituted by from 1 to 3 of substituents α and substituents γ or such a substituted or unsubstituted alkyl group in which the carbon chain is interrupted by an oxygen atom and/or a sulphur atom;

(D) A is a group of formula $-CON(R^2)SO_2-$, [in which, R^2 is a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or a benzyl group];

(E) B represents a single bond, or a group of formula $-N(R^5)-$ or $-N(R^5)N(R^6)-$ [in which R^5 and R^6 are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or a benzyl group];

[0056] Of the above, we particularly prefer those compounds of formula (I) in which m and n are as defined in (A) above, k is as defined in (B) above, R^1 is as defined in (C) above, A is as defined in (D) above, and B is as defined in (E) above.

[0057] More preferred compounds of the present invention are those compounds of formula (I) and salts thereof in which:

(F) both of m and n are 0;

(G) k is an integer of from 2 to 6;

(H) R^1 represents an alkyl group having from 1 to 5 carbon atoms, an alkoxycarbonylalkyl group having from 3 to 8 carbon atoms, a carboxyalkyl group having from 2 to 7 carbon atoms, a hydroxyalkyl group having from 2 to 5 carbon atoms, a heterocyclic group, an alkoxy group having from 1 to 5 carbon atoms or a hydroxy group;

(I) A represents a group of formula $-CON(R^2)SO_2-$, [in which, R^2 represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms]

(J) B represents a single bond, or a group of formula $-N(R^5)-$ or $-N(R^5)N(R^6)-$ [in which R^5 and R^6 are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms];

[0058] Of the above, we particularly prefer those compounds of formula (I) in which m and n are as defined in (F) above, k is as defined in (G) above, R^1 is as defined in (H) above, A is as defined in (I) above, and B is as defined in

(J) above.

[0059] The most preferred compounds of the present invention are those compounds of formula (I) and salts thereof in which:

(K) both of m and n are 0;

(L) k is 4 or 5;

(M) R^1 represents an alkyl group having from 1 to 5 carbon atoms, an alkoxycarbonylalkyl group having from 3 to 8 carbon atoms, a carboxyalkyl group having from 2 to 7 carbon atoms, a hydroxyalkyl group having from 2 to 5 carbon atoms, a heterocyclic group or an alkoxy group having from 1 to 5 carbon atoms;

(N) A represents a group of formula $-CONHSO_2-$, or $-CONCH_3SO_2$,

(O) B represents a single bond, or a group of formula -NH-, $-NCH_3-$ or $-NHNCH_3-$;

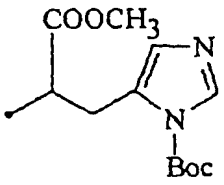
[0060] Of the above, we particularly prefer those compounds of formula (I) in which m and n are as defined in (K) above, k is as defined in (L) above, R^1 is as defined in (M) above, A is as defined in (N) above, and B is as defined in (O) above.

[0061] Specific examples of individual compounds of the present invention are shown in the following formulae (I-1), (1-2) and (I-3), in which the substituent groups are as shown in the corresponding one of Tables 1 to 3. In the Tables, the following abbreviations are used:

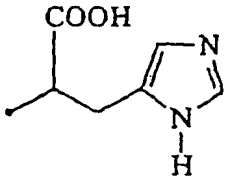
Ac	acetyl;
Bu	butyl;
*i*Bu	isobutyl;
*s*Bu	sec-butyl;
*t*Bu	t-butyl;
Bz	benzyl;
1,3-diox-IInd	isoindol-1,3-dione-2-yl;
3,4-diMe-2,5-diox-1-Imdd	3,4-dimethyl-imidazolidin-2,5-dione-1yl;
Et	ethyl;
Hx	hexyl;
Indn	indolinyl;
Me	methyl;
Mor	morpholino;
Ph	phenyl;
Pipra	piperazino;
Pipri	piperidino;
Pn	pentyl;
*i*Pn	isopentyl;
Pr	propyl;
*i*Pr	isopropyl;
Py	pyridyl;
Pyr	pyrrolidinyl;
Thiad	3-thiazolidinyl;
Thmor	thiomorpholino.

[0062] Also, in the Tables, the groups represented by Z-1 to Z-12 have the following formulae:

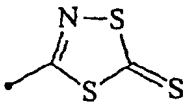
Z-1



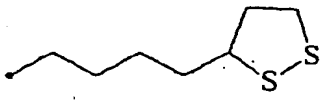
Z-2



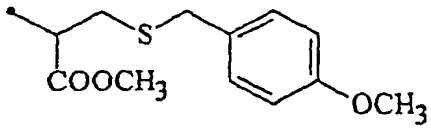
Z-3



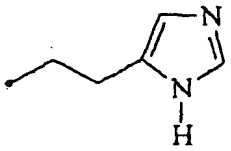
Z-4



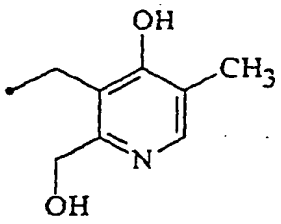
Z-5



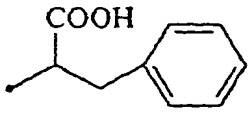
Z-6



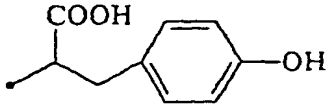
Z-7



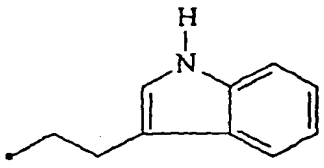
Z-8



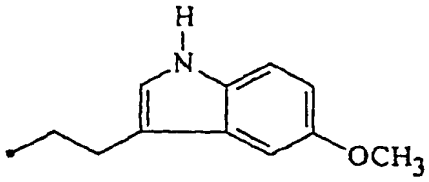
Z-9



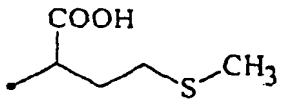
Z-10

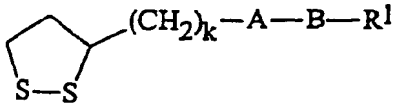


Z-11



Z-12





(I-1)

Table 1

Cpd. No.	k	A	B	R^1
1-456	4	$CONHSO_2$	—	H
1-457	4	$CONHSO_2$	—	Ph
1-458	4	$CONHSO_2$	—	2-Me-Ph
1-459	4	$CONHSO_2$	—	4-Me-Ph
1-460	4	$CONHSO_2$	—	2,4-diMe-Ph
1-461	4	$CONHSO_2$	—	3,4-diMe-Ph
1-462	4	$CONHSO_2$	—	2-(CF_3)Ph
1-463	4	$CONHSO_2$	—	4-(CF_3)Ph
1-464	4	$CONHSO_2$	—	2-MeOPh
1-465	4	$CONHSO_2$	—	4-MeOPh
1-466	4	$CONHSO_2$	—	2-EtOPh
1-467	4	$CONHSO_2$	—	4-EtOPh
1-468	4	$CONHSO_2$	—	2-HOPh
1-469	4	$CONHSO_2$	—	4-HOPh
1-470	4	$CONHSO_2$	—	2-(HOOC)Ph
1-471	4	$CONHSO_2$	—	4-(HOOC)Ph
1-472	4	$CONHSO_2$	—	2-(MeOOC)Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-473	4	$CONHSO_2$	—	4-(MeOOC)Ph
1-474	4	$CONHSO_2$	—	2-(EtOOC)Ph
1-475	4	$CONHSO_2$	—	4-(EtOOC)Ph
1-476	4	$CONHSO_2$	—	2-(*t*BuOOC)Ph
1-477	4	$CONHSO_2$	—	4-(*t*BuOOC)Ph
1-478	4	$CONHSO_2$	—	2-Cl-Ph
1-479	4	$CONHSO_2$	—	4-Cl-Ph
1-480	4	$CONHSO_2$	—	2-Br-Ph
1-481	4	$CONHSO_2$	—	4-Br-Ph
1-482	4	$CONHSO_2$	—	2-I-Ph
1-483	4	$CONHSO_2$	—	4-I-Ph
1-484	4	$CONHSO_2$	—	2-NO_2-Ph
1-485	4	$CONHSO_2$	—	4-NO_2-Ph
1-486	4	$CONHSO_2$	—	2-NH_2-Ph
1-487	4	$CONHSO_2$	—	4-NH_2-Ph
1-488	4	$CONHSO_2$	—	2-(HO_3S)Ph
1-489	4	$CONHSO_2$	—	4-(HO_3S)Ph
1-490	4	$CONHSO_2$	—	2-(NH_2O_2S)Ph
1-491	4	$CONHSO_2$	—	4-(NH_2O_2S)Ph
1-492	4	$CONHSO_2$	—	2-CN-Ph
1-493	4	$CONHSO_2$	—	4-CN-Ph
1-494	4	$CONHSO_2$	—	2-($HOCH_2$)Ph
1-495	4	$CONHSO_2$	—	4-($HOCH_2$)Ph
1-496	4	$CONHSO_2$	—	Me

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-497	4	$CONHSO_2$	—	Et
1-498	4	$CONHSO_2$	—	Pr
1-499	4	$CONHSO_2$	—	*i*Pr
1-500	4	$CONHSO_2$	—	Bu
1-501	4	$CONHSO_2$	—	$HOOCCH_2$-
1-502	4	$CONHSO_2$	—	$MeOOCCH_2$-
1-503	4	$CONHSO_2$	—	MeCH(COOH)
1-504	4	$CONHSO_2$	—	HOOC-$(CH_2)_2$-
1-505	4	$CONHSO_2$	—	MeCH(COOMe)
1-506	4	$CONHSO_2$	—	1-HOOC-*i*Bu
1-507	4	$CONHSO_2$	—	1-MeOOC-*i*Bu
1-508	4	$CONHSO_2$	—	1-HOOC-*i*Pn
1-509	4	$CONHSO_2$	—	1-MeOOC-*i*Pn
1-510	4	$CONHSO_2$	—	1-HOOC-2-Me-Bu
1-511	4	$CONHSO_2$	—	1-MeOOC-2-Me-Bu
1-512	4	$CONHSO_2$	—	$CH_2CH_2SO_3H$
1-513	4	$CONHSO_2$	—	OH
1-514	4	$CONHSO_2$	—	MeO
1-515	4	$CONHSO_2$	—	EtO
1-516	4	$CONHSO_2$	—	PrO
1-517	4	$CONHSO_2$	—	*i*PrO
1-518	4	$CONHSO_2$	—	BuO
1-519	4	$CONHSO_2$	—	*i*BuO
1-520	4	$CONHSO_2$	—	*s*BuO

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-521	4	$CONHSO_2$	—	*t*BuO
1-522	4	$CONHSO_2$	—	HxO
1-523	4	$CONHSO_2$	—	PhO
1-524	4	$CONHSO_2$	—	BzO
1-525	4	$CONHSO_2$	—	Z-1
1-526	4	$CONHSO_2$	—	Z-2
1-527	4	$CONHSO_2$	—	Z-3
1-528	4	$CONHSO_2$	—	Z-4
1-529	4	$CONHSO_2$	—	Z-5
1-530	4	$CONHSO_2$	—	Z-6
1-531	4	$CONHSO_2$	—	Z-7
1-532	4	$CONHSO_2$	—	Z-8
1-533	4	$CONHSO_2$	—	Z-9
1-534	4	$CONHSO_2$	—	Z-10
1-535	4	$CONHSO_2$	—	Z-11
1-536	4	$CONHSO_2$	—	Z-12
1-537	4	$CONHSO_2$	—	3-Py
1-538	4	$CONHSO_2$	—	4-Py
1-539	4	$CONHSO_2$	NH	H
1-540	4	$CONHSO_2$	NH	Ph
1-541	4	$CONHSO_2$	NH	2-Me-Ph
1-542	4	$CONHSO_2$	NH	4-Me-Ph
1-543	4	$CONHSO_2$	NH	2.4-diMe-Ph
1-544	4	$CONHSO_2$	NH	3.4-diMe-Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-545	4	$CONHSO_2$	NH	2-(CF_3)Ph
1-546	4	$CONHSO_2$	NH	4-(CF_3)Ph
1-547	4	$CONHSO_2$	NH	2-MeOPh
1-548	4	$CONHSO_2$	NH	4-MeOPh
1-549	4	$CONHSO_2$	NH	2-EtOPh
1-550	4	$CONHSO_2$	NH	4-EtOPh
1-551	4	$CONHSO_2$	NH	2-HOPh
1-552	4	$CONHSO_2$	NH	4-HOPh
1-553	4	$CONHSO_2$	NH	2-(HOOC)Ph
1-554	4	$CONHSO_2$	NH	4-(HOOC)Ph
1-555	4	$CONHSO_2$	NH	2-(MeOOC)Ph
1-556	4	$CONHSO_2$	NH	4-(MeOOC)Ph
1-557	4	$CONHSO_2$	NH	2-(EtOOC)Ph
1-558	4	$CONHSO_2$	NH	4-(EtOOC)Ph
1-559	4	$CONHSO_2$	NH	2-(*t*BuOOC)Ph
1-560	4	$CONHSO_2$	NH	4-(*t*BuOOC)Ph
1-561	4	$CONHSO_2$	NH	2-Cl-Ph
1-562	4	$CONHSO_2$	NH	4-Cl-Ph
1-563	4	$CONHSO_2$	NH	2-Br-Ph
1-564	4	$CONHSO_2$	NH	4-Br-Ph
1-565	4	$CONHSO_2$	NH	2-I-Ph
1-566	4	$CONHSO_2$	NH	4-I-Ph
1-567	4	$CONHSO_2$	NH	2-NO_2-Ph
1-568	4	$CONHSO_2$	NH	4-NO_2-Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-569	4	$CONHSO_2$	NH	2-NH_2-Ph
1-570	4	$CONHSO_2$	NH	4-NH_2-Ph
1-571	4	$CONHSO_2$	NH	2-(HO_3S)Ph
1-572	4	$CONHSO_2$	NH	4-(HO_3S)Ph
1-573	4	$CONHSO_2$	NH	2-(NH_2O_2S)Ph
1-574	4	$CONHSO_2$	NH	4-(NH_2O_2S)Ph
1-575	4	$CONHSO_2$	NH	2-CN-Ph
1-576	4	$CONHSO_2$	NH	4-CN-Ph
1-577	4	$CONHSO_2$	NH	2-($HOCH_2$)Ph
1-578	4	$CONHSO_2$	NH	4-($HOCH_2$)Ph
1-579	4	$CONHSO_2$	NH	Me
1-580	4	$CONHSO_2$	NH	Et
1-581	4	$CONHSO_2$	NH	Pr
1-582	4	$CONHSO_2$	NH	*i*Pr
1-583	4	$CONHSO_2$	NH	Bu
1-584	4	$CONHSO_2$	NH	$HOOCCH_2$-
1-585	4	$CONHSO_2$	NH	$MeOOCCH_2$-
1-586	4	$CONHSO_2$	NH	MeCH(COOH)
1-587	4	$CONHSO_2$	NH	HOOC-$(CH_2)_2$-
1-588	4	$CONHSO_2$	NH	MeCH(COOMe)
1-589	4	$CONHSO_2$	NH	1-HOOC-*i*Bu
1-590	4	$CONHSO_2$	NH	1-MeOOC-*i*Bu
1-591	4	$CONHSO_2$	NH	1-HOOC-*i*Pn
1-592	4	$CONHSO_2$	NH	1-MeOOC-*i*Pn

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-593	4	$CONHSO_2$	NH	1-HOOC-2-Me-Bu
1-594	4	$CONHSO_2$	NH	1-MeOOC-2-Me-Bu
1-595	4	$CONHSO_2$	NH	$CH_2CH_2SO_3H$
1-596	4	$CONHSO_2$	NH	OH
1-597	4	$CONHSO_2$	NH	MeO
1-598	4	$CONHSO_2$	NH	EtO
1-599	4	$CONHSO_2$	NH	PrO
1-600	4	$CONHSO_2$	NH	*i*PrO
1-601	4	$CONHSO_2$	NH	BuO
1-602	4	$CONHSO_2$	NH	*i*BuO
1-603	4	$CONHSO_2$	NH	*s*BuO
1-604	4	$CONHSO_2$	NH	*t*BuO
1-605	4	$CONHSO_2$	NH	HxO
1-606	4	$CONHSO_2$	NH	PhO
1-607	4	$CONHSO_2$	NH	BzO
1-608	4	$CONHSO_2$	NH	Z-1
1-609	4	$CONHSO_2$	NH	Z-2
1-610	4	$CONHSO_2$	NH	Z-3
1-611	4	$CONHSO_2$	NH	Z-4
1-612	4	$CONHSO_2$	NH	Z-5
1-613	4	$CONHSO_2$	NH	Z-6
1-614	4	$CONHSO_2$	NH	Z-7
1-615	4	$CONHSO_2$	NH	Z-8
1-616	4	$CONHSO_2$	NH	Z-9

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-617	4	$CONHSO_2$	NH	Z-10
1-618	4	$CONHSO_2$	NH	Z-11
1-619	4	$CONHSO_2$	NH	Z-12
1-620	4	$CONHSO_2$	NH	3-Py
1-621	4	$CONHSO_2$	NH	4-Py

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1159	4	$CONHSO_2$	Pyr	
1-1160	4	$CONHSO_2$	Pipri	
1-1161	4	$CONHSO_2$	Pipra	
1-1162	4	$CONHSO_2$	Mor	
1-1163	4	$CONHSO_2$	Thmor	

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1164	4	$CONHSO_2$	NHPyr	
1-1165	4	$CONHSO_2$	NHPipri	
1-1166	4	$CONHSO_2$	NHPipra	
1-1167	4	$CONHSO_2$	NHMor	
1-1168	4	$CONHSO_2$	NHThmor	

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1264	4	$CONHSO_2$	Thiad	
1-1265	4	$CONHSO_2$	NHThiad	

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1756	5	$CONHSO_2$	—	H
1-1757	5	$CONHSO_2$	—	Ph
1-1758	5	$CONHSO_2$	—	2-Me-Ph
1-1759	5	$CONHSO_2$	—	4-Me-Ph
1-1760	5	$CONHSO_2$	—	2,4-diMe-Ph
1-1761	5	$CONHSO_2$	—	3,4-diMe-Ph
1-1762	5	$CONHSO_2$	—	2-(CF_3)Ph
1-1763	5	$CONHSO_2$	—	4-(CF_3)Ph
1-1764	5	$CONHSO_2$	—	2-MeOPh
1-1765	5	$CONHSO_2$	—	4-MeOPh
1-1766	5	$CONHSO_2$	—	2-EtOPh
1-1767	5	$CONHSO_2$	—	4-EtOPh
1-1768	5	$CONHSO_2$	—	2-HOPh
1-1769	5	$CONHSO_2$	—	4-HOPh
1-1770	5	$CONHSO_2$	—	2-(HOOC)Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1771	5	$CONHSO_2$	—	4-(HOOC)Ph
1-1772	5	$CONHSO_2$	—	2-(MeOOC)Ph
1-1773	5	$CONHSO_2$	—	4-(MeOOC)Ph
1-1774	5	$CONHSO_2$	—	2-(EtOOC)Ph
1-1775	5	$CONHSO_2$	—	4-(EtOOC)Ph
1-1776	5	$CONHSO_2$	—	2-(*t*BuOOC)Ph
1-1777	5	$CONHSO_2$	—	4-(*t*BuOOC)Ph
1-1778	5	$CONHSO_2$	—	2-Cl-Ph
1-1779	5	$CONHSO_2$	—	4-Cl-Ph
1-1780	5	$CONHSO_2$	—	2-Br-Ph
1-1781	5	$CONHSO_2$	—	4-Br-Ph
1-1782	5	$CONHSO_2$	—	2-I-Ph
1-1783	5	$CONHSO_2$	—	4-I-Ph
1-1784	5	$CONHSO_2$	—	2-NO_2-Ph
1-1785	5	$CONHSO_2$	—	4-NO_2-Ph
1-1786	5	$CONHSO_2$	—	2-NH_2-Ph
1-1787	5	$CONHSO_2$	—	4-NH_2-Ph
1-1788	5	$CONHSO_2$	—	2-(HO_3S)Ph
1-1789	5	$CONHSO_2$	—	4-(HO_3S)Ph
1-1790	5	$CONHSO_2$	—	2-(NH_2O_2S)Ph
1-1791	5	$CONHSO_2$	—	4-(NH_2O_2S)Ph
1-1792	5	$CONHSO_2$	—	2-CN-Ph
1-1793	5	$CONHSO_2$	—	4-CN-Ph
1-1794	5	$CONHSO_2$	—	2-($HOCH_2$)Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1795	5	$CONHSO_2$	—	4-($HOCH_2$)Ph
1-1796	5	$CONHSO_2$	—	Me
1-1797	5	$CONHSO_2$	—	Et
1-1798	5	$CONHSO_2$	—	Pr
1-1799	5	$CONHSO_2$	—	*i*Pr
1-1800	5	$CONHSO_2$	—	Bu
1-1801	5	$CONHSO_2$	—	$HOOCCH_2$-
1-1802	5	$CONHSO_2$	—	$MeOOCCH_2$-
1-1803	5	$CONHSO_2$	—	MeCH(COOH)
1-1804	5	$CONHSO_2$	—	HOOC-$(CH_2)_2$-
1-1805	5	$CONHSO_2$	—	MeCH(COOMe)
1-1806	5	$CONHSO_2$	—	1-HOOC-*i*Bu
1-1807	5	$CONHSO_2$	—	1-MeOOC-*i*Bu
1-1808	5	$CONHSO_2$	—	1-HOOC-*i*Pn
1-1809	5	$CONHSO_2$	—	1-MeOOC-*i*Pn
1-1810	5	$CONHSO_2$	—	1-HOOC-2-Me-Bu
1-1811	5	$CONHSO_2$	—	1-MeOOC-2-Me-Bu
1-1812	5	$CONHSO_2$	—	$CH_2CH_2SO_3H$
1-1813	5	$CONHSO_2$	—	OH
1-1814	5	$CONHSO_2$	—	MeO
1-1815	5	$CONHSO_2$	—	EtO
1-1816	5	$CONHSO_2$	—	PrO
1-1817	5	$CONHSO_2$	—	*i*PrO
1-1818	5	$CONHSO_2$	—	BuO

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1819	5	$CONHSO_2$	—	*i*BuO
1-1820	5	$CONHSO_2$	—	*s*BuO
1-1821	5	$CONHSO_2$	—	*t*BuO
1-1822	5	$CONHSO_2$	—	HxO
1-1823	5	$CONHSO_2$	—	PhO
1-1824	5	$CONHSO_2$	—	BzO
1-1825	5	$CONHSO_2$	—	Z-1
1-1826	5	$CONHSO_2$	—	Z-2
1-1827	5	$CONHSO_2$	—	Z-3
1-1828	5	$CONHSO_2$	—	Z-4
1-1829	5	$CONHSO_2$	—	Z-5
1-1830	5	$CONHSO_2$	—	Z-6
1-1831	5	$CONHSO_2$	—	Z-7
1-1832	5	$CONHSO_2$	—	Z-8
1-1833	5	$CONHSO_2$	—	Z-9
1-1834	5	$CONHSO_2$	—	Z-10
1-1835	5	$CONHSO_2$	—	Z-11
1-1836	5	$CONHSO_2$	—	Z-12
1-1837	5	$CONHSO_2$	—	3-Py
1-1838	5	$CONHSO_2$	—	4-Py
1-1839	5	$CONHSO_2$	NH	H
1-1840	5	$CONHSO_2$	NH	Ph
1-1841	5	$CONHSO_2$	NH	2-Me-Ph
1-1842	5	$CONHSO_2$	NH	4-Me-Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1843	5	$CONHSO_2$	NH	2,4-diMe-Ph
1-1844	5	$CONHSO_2$	NH	3,4-diMe-Ph
1-1845	5	$CONHSO_2$	NH	2-(CF_3)Ph
1-1846	5	$CONHSO_2$	NH	4-(CF_3)Ph
1-1847	5	$CONHSO_2$	NH	2-MeOPh
1-1848	5	$CONHSO_2$	NH	4-MeOPh
1-1849	5	$CONHSO_2$	NH	2-EtOPh
1-1850	5	$CONHSO_2$	NH	4-EtOPh
1-1851	5	$CONHSO_2$	NH	2-HOPh
1-1852	5	$CONHSO_2$	NH	4-HOPh
1-1853	5	$CONHSO_2$	NH	2-(HOOC)Ph
1-1854	5	$CONHSO_2$	NH	4-(HOOC)Ph
1-1855	5	$CONHSO_2$	NH	2-(MeOOC)Ph
1-1856	5	$CONHSO_2$	NH	4-(MeOOC)Ph
1-1857	5	$CONHSO_2$	NH	2-(EtOOC)Ph
1-1858	5	$CONHSO_2$	NH	4-(EtOOC)Ph
1-1859	5	$CONHSO_2$	NH	2-(*t*BuOOC)Ph
1-1860	5	$CONHSO_2$	NH	4-(*t*BuOOC)Ph
1-1861	5	$CONHSO_2$	NH	2-Cl-Ph
1-1862	5	$CONHSO_2$	NH	4-Cl-Ph
1-1863	5	$CONHSO_2$	NH	2-Br-Ph
1-1864	5	$CONHSO_2$	NH	4-Br-Ph
1-1865	5	$CONHSO_2$	NH	2-I-Ph
1-1866	5	$CONHSO_2$	NH	4-I-Ph

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1867	5	$CONHSO_2$	NH	2-NO_2-Ph
1-1868	5	$CONHSO_2$	NH	4-NO_2-Ph
1-1869	5	$CONHSO_2$	NH	2-NH_2-Ph
1-1870	5	$CONHSO_2$	NH	4-NH_2-Ph
1-1871	5	$CONHSO_2$	NH	2-(HO_3S)Ph
1-1872	5	$CONHSO_2$	NH	4-(HO_3S)Ph
1-1873	5	$CONHSO_2$	NH	2-(NH_2O_2S)Ph
1-1874	5	$CONHSO_2$	NH	4-(NH_2O_2S)Ph
1-1875	5	$CONHSO_2$	NH	2-CN-Ph
1-1876	5	$CONHSO_2$	NH	4-CN-Ph
1-1877	5	$CONHSO_2$	NH	2-($HOCH_2$)Ph
1-1878	5	$CONHSO_2$	NH	4-($HOCH_2$)Ph
1-1879	5	$CONHSO_2$	NH	Me
1-1880	5	$CONHSO_2$	NH	Et
1-1881	5	$CONHSO_2$	NH	Pr
1-1882	5	$CONHSO_2$	NH	*i*Pr
1-1883	5	$CONHSO_2$	NH	Bu
1-1884	5	$CONHSO_2$	NH	$HOOCCH_2$-
1-1885	5	$CONHSO_2$	NH	$MeOOCCH_2$-
1-1886	5	$CONHSO_2$	NH	MeCH(COOH)
1-1887	5	$CONHSO_2$	NH	HOOC-$(CH_2)_2$-
1-1888	5	$CONHSO_2$	NH	MeCH(COOMe)
1-1889	5	$CONHSO_2$	NH	1-HOOC-*i*Bu
1-1890	5	$CONHSO_2$	NH	1-MeOOC-*i*Bu

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1891	5	$CONHSO_2$	NH	1-HOOC-*i*Pn
1-1892	5	$CONHSO_2$	NH	1-MeOOC-*i*Pn
1-1893	5	$CONHSO_2$	NH	1-HOOC-2-Me-Bu
1-1894	5	$CONHSO_2$	NH	1-MeOOC-2-Me-Bu
1-1895	5	$CONHSO_2$	NH	$CH_2CH_2SO_3H$
1-1896	5	$CONHSO_2$	NH	OH
1-1897	5	$CONHSO_2$	NH	MeO
1-1898	5	$CONHSO_2$	NH	EtO
1-1899	5	$CONHSO_2$	NH	PrO
1-1900	5	$CONHSO_2$	NH	*i*PrO
1-1901	5	$CONHSO_2$	NH	BuO
1-1902	5	$CONHSO_2$	NH	*i*BuO
1-1903	5	$CONHSO_2$	NH	*s*BuO
1-1904	5	$CONHSO_2$	NH	*t*BuO
1-1905	5	$CONHSO_2$	NH	HxO
1-1906	5	$CONHSO_2$	NH	PhO
1-1907	5	$CONHSO_2$	NH	BzO
1-1908	5	$CONHSO_2$	NH	Z-1
1-1909	5	$CONHSO_2$	NH	Z-2
1-1910	5	$CONHSO_2$	NH	Z-3
1-1911	5	$CONHSO_2$	NH	Z-4
1-1912	5	$CONHSO_2$	NH	Z-5
1-1913	5	$CONHSO_2$	NH	Z-6
1-1914	5	$CONHSO_2$	NH	Z-7

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-1915	5	$CONHSO_2$	NH	Z-8
1-1916	5	$CONHSO_2$	NH	Z-9
1-1917	5	$CONHSO_2$	NH	Z-10
1-1918	5	$CONHSO_2$	NH	Z-11
1-1919	5	$CONHSO_2$	NH	Z-12
1-1920	5	$CONHSO_2$	NH	3-Py
1-1921	5	$CONHSO_2$	NH	4-Py

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-2459	5	$CONHSO_2$	Pyr	
1-2460	5	$CONHSO_2$	Pipri	
1-2461	5	$CONHSO_2$	Pipra	
1-2462	5	$CONHSO_2$	Mor	
1-2463	5	$CONHSO_2$	Thmor	

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-2464	5	$CONHSO_2$	NHPyr	
1-2465	5	$CONHSO_2$	NHPipri	
1-2466	5	$CONHSO_2$	NHPipra	
1-2467	5	$CONHSO_2$	NHMor	
1-2468	5	$CONHSO_2$	NHThmor	

Table 1 (cont.)

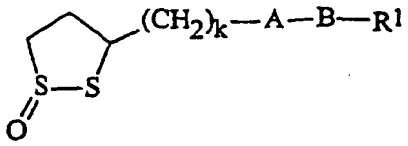
Cpd. No.	k	A	B	R^1
1-2564	5	$CONHSO_2$	Thiad	
1-2565	5	$CONHSO_2$	NHThiad	

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-2672	4	$CONMeSO_2$	—	Me

Table 1 (cont.)

Cpd. No.	k	A	B	R^1
1-2673	5	$CONMeSO_2$	—	Me
1-2684	4	$CONHSO_2$	—	CF_3



(I-2)

Table 2

Cpd. No.	k	A	B	R^1
2-456	4	$CONHSO_2$	—	H
2-457	4	$CONHSO_2$	—	Ph
2-458	4	$CONHSO_2$	—	2-Me-Ph
2-459	4	$CONHSO_2$	—	4-Me-Ph
2-460	4	$CONHSO_2$	—	2,4-diMe-Ph
2-461	4	$CONHSO_2$	—	3,4-diMe-Ph
2-462	4	$CONHSO_2$	—	2-(CF_3)Ph
2-463	4	$CONHSO_2$	—	4-(CF_3)Ph

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-464	4	$CONHSO_2$	—	2-MeOPh
2-465	4	$CONHSO_2$	—	4-MeOPh
2-466	4	$CONHSO_2$	—	2-EtOPh
2-467	4	$CONHSO_2$	—	4-EtOPh
2-468	4	$CONHSO_2$	—	2-HOPh
2-469	4	$CONHSO_2$	—	4-HOPh
2-470	4	$CONHSO_2$	—	2-(HOOC)Ph
2-471	4	$CONHSO_2$	—	4-(HOOC)Ph
2-472	4	$CONHSO_2$	—	2-(MeOOC)Ph
2-473	4	$CONHSO_2$	—	4-(MeOOC)Ph
2-474	4	$CONHSO_2$	—	2-(EtOOC)Ph
2-475	4	$CONHSO_2$	—	4-(EtOOC)Ph
2-476	4	$CONHSO_2$	—	2-(*t*BuOOC)Ph
2-477	4	$CONHSO_2$	—	4-(*t*BuOOC)Ph
2-478	4	$CONHSO_2$	—	2-Cl-Ph
2-479	4	$CONHSO_2$	—	4-Cl-Ph
2-480	4	$CONHSO_2$	—	2-Br-Ph
2-481	4	$CONHSO_2$	—	4-Br-Ph
2-482	4	$CONHSO_2$	—	2-I-Ph
2-483	4	$CONHSO_2$	—	4-I-Ph
2-484	4	$CONHSO_2$	—	2-NO_2-Ph
2-485	4	$CONHSO_2$	—	4-NO_2-Ph
2-486	4	$CONHSO_2$	—	2-NH_2-Ph
2-487	4	$CONHSO_2$	—	4-NH_2-Ph
2-488	4	$CONHSO_2$	—	2-(HO_3S)Ph

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-489	4	$CONHSO_2$	—	4-(HO_3S)Ph
2-490	4	$CONHSO_2$	—	2-(NH_2O_2S)Ph
2-491	4	$CONHSO_2$	—	4-(NH_2O_2S)Ph
2-492	4	$CONHSO_2$	—	2-CN-Ph
2-493	4	$CONHSO_2$	—	4-CN-Ph
2-494	4	$CONHSO_2$	—	2-($HOCH_2$)Ph
2-495	4	$CONHSO_2$	—	4-($HOCH_2$)Ph
2-496	4	$CONHSO_2$	—	Me
2-497	4	$CONHSO_2$	—	Et
2-498	4	$CONHSO_2$	—	Pr
2-499	4	$CONHSO_2$	—	*i*Pr
2-500	4	$CONHSO_2$	—	Bu
2-501	4	$CONHSO_2$	—	$HOOCCH_2$-
2-502	4	$CONHSO_2$	—	$MeOOCCH_2$-
2-503	4	$CONHSO_2$	—	MeCH(COOH)
2-504	4	$CONHSO_2$	—	HOOC-$(CH_2)_2$-
2-505	4	$CONHSO_2$	—	MeCH(COOMe)
2-506	4	$CONHSO_2$	—	1-HOOC-*i*Bu
2-507	4	$CONHSO_2$	—	1-MeOOC-*i*Bu
2-508	4	$CONHSO_2$	—	1-HOOC-*i*Pn
2-509	4	$CONHSO_2$	—	1-MeOOC-*i*Pn
2-510	4	$CONHSO_2$	—	1-HOOC-2-Me-Bu
2-511	4	$CONHSO_2$	—	1-MeOOC-2-Me-Bu
2-512	4	$CONHSO_2$	—	$CH_2CH_2SO_3H$
2-513	4	$CONHSO_2$	—	OH

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-514	4	$CONHSO_2$	—	MeO
2-515	4	$CONHSO_2$	—	EtO
2-516	4	$CONHSO_2$	—	PrO
2-517	4	$CONHSO_2$	—	*i*PrO
2-518	4	$CONHSO_2$	—	BuO
2-519	4	$CONHSO_2$	—	*i*BuO
2-520	4	$CONHSO_2$	—	*s*BuO
2-521	4	$CONHSO_2$	—	*t*BuO
2-522	4	$CONHSO_2$	—	HxO
2-523	4	$CONHSO_2$	—	PhO
2-524	4	$CONHSO_2$	—	BnO
2-525	4	$CONHSO_2$	—	Z-1
2-526	4	$CONHSO_2$	—	Z-2
2-527	4	$CONHSO_2$	—	Z-3
2-528	4	$CONHSO_2$	—	Z-4
2-529	4	$CONHSO_2$	—	Z-5
2-530	4	$CONHSO_2$	—	Z-6
2-531	4	$CONHSO_2$	—	Z-7
2-532	4	$CONHSO_2$	—	Z-8
2-533	4	$CONHSO_2$	—	Z-9
2-534	4	$CONHSO_2$	—	Z-10
2-535	4	$CONHSO_2$	—	Z-11
2-536	4	$CONHSO_2$	—	Z-12
2-537	4	$CONHSO_2$	—	3-Py
2-538	4	$CONHSO_2$	—	4-Py

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-539	4	$CONHSO_2$	NH	H
2-540	4	$CONHSO_2$	NH	Ph
2-541	4	$CONHSO_2$	NH	2-Me-Ph
2-542	4	$CONHSO_2$	NH	4-Me-Ph
2-543	4	$CONHSO_2$	NH	2,4-diMe-Ph
2-544	4	$CONHSO_2$	NH	3,4-diMe-Ph
2-545	4	$CONHSO_2$	NH	2-(CF_3)Ph
2-546	4	$CONHSO_2$	NH	4-(CF_3)Ph
2-547	4	$CONHSO_2$	NH	2-MeOPh
2-548	4	$CONHSO_2$	NH	4-MeOPh
2-549	4	$CONHSO_2$	NH	2-EtOPh
2-550	4	$CONHSO_2$	NH	4-EtOPh
2-551	4	$CONHSO_2$	NH	2-HOPh
2-552	4	$CONHSO_2$	NH	4-HOPh
2-553	4	$CONHSO_2$	NH	2-(HOOC)Ph
2-554	4	$CONHSO_2$	NH	4-(HOOC)Ph
2-555	4	$CONHSO_2$	NH	2-(MeOOC)Ph
2-556	4	$CONHSO_2$	NH	4-(MeOOC)Ph
2-557	4	$CONHSO_2$	NH	2-(EtOOC)Ph
2-558	4	$CONHSO_2$	NH	4-(EtOOC)Ph
2-559	4	$CONHSO_2$	NH	2-(*t*BuOOC)Ph
2-560	4	$CONHSO_2$	NH	4-(*t*BuOOC)Ph
2-561	4	$CONHSO_2$	NH	2-Cl-Ph
2-562	4	$CONHSO_2$	NH	4-Cl-Ph
2-563	4	$CONHSO_2$	NH	2-Br-Ph

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-564	4	$CONHSO_2$	NH	4-Br-Ph
2-565	4	$CONHSO_2$	NH	2-I-Ph
2-566	4	$CONHSO_2$	NH	4-I-Ph
2-567	4	$CONHSO_2$	NH	2-NO_2-Ph
2-568	4	$CONHSO_2$	NH	4-NO_2-Ph
2-569	4	$CONHSO_2$	NH	2-NH_2-Ph
2-570	4	$CONHSO_2$	NH	4-NH_2-Ph
2-571	4	$CONHSO_2$	NH	2-(HO_3S)Ph
2-572	4	$CONHSO_2$	NH	4-(HO_3S)Ph
2-573	4	$CONHSO_2$	NH	2-(NH_2O_2S)Ph
2-574	4	$CONHSO_2$	NH	4-(NH_2O_2S)Ph
2-575	4	$CONHSO_2$	NH	2-CN-Ph
2-576	4	$CONHSO_2$	NH	4-CN-Ph
2-577	4	$CONHSO_2$	NH	2-($HOCH_2$)Ph
2-578	4	$CONHSO_2$	NH	4-($HOCH_2$)Ph
2-579	4	$CONHSO_2$	NH	Me
2-580	4	$CONHSO_2$	NH	Et
2-581	4	$CONHSO_2$	NH	Pr
2-582	4	$CONHSO_2$	NH	*i*Pr
2-583	4	$CONHSO_2$	NH	Bu
2-584	4	$CONHSO_2$	NH	$HOOCCH_2$-
2-585	4	$CONHSO_2$	NH	$MeOOCCH_2$-
2-586	4	$CONHSO_2$	NH	MeCH(COOH)
2-587	4	$CONHSO_2$	NH	HOOC-$(CH_2)_2$-
2-588	4	$CONHSO_2$	NH	MeCH(COOMe)

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-589	4	$CONHSO_2$	NH	1-HOOC-*i*Bu
2-590	4	$CONHSO_2$	NH	1-MeOOC-*i*Bu
2-591	4	$CONHSO_2$	NH	1-HOOC-*i*Pn
2-592	4	$CONHSO_2$	NH	1-MeOOC-*i*Pn
2-593	4	$CONHSO_2$	NH	1-HOOC-2-Me-Bu
2-594	4	$CONHSO_2$	NH	1-MeOOC-2-Me-Bu
2-595	4	$CONHSO_2$	NH	$CH_2CH_2SO_3H$
2-596	4	$CONHSO_2$	NH	OH
2-597	4	$CONHSO_2$	NH	MeO
2-598	4	$CONHSO_2$	NH	EtO
2-599	4	$CONHSO_2$	NH	PrO
2-600	4	$CONHSO_2$	NH	*i*PrO
2-601	4	$CONHSO_2$	NH	BuO
2-602	4	$CONHSO_2$	NH	*i*BuO
2-603	4	$CONHSO_2$	NH	*s*BuO
2-604	4	$CONHSO_2$	NH	*t*BuO
2-605	4	$CONHSO_2$	NH	HxO
2-606	4	$CONHSO_2$	NH	PhO
2-607	4	$CONHSO_2$	NH	BnO
2-608	4	$CONHSO_2$	NH	Z-1
2-609	4	$CONHSO_2$	NH	Z-2
2-610	4	$CONHSO_2$	NH	Z-3
2-611	4	$CONHSO_2$	NH	Z-4
2-612	4	$CONHSO_2$	NH	Z-5
2-613	4	$CONHSO_2$	NH	Z-6

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-614	4	$CONHSO_2$	NH	Z-7
2-615	4	$CONHSO_2$	NH	Z-8
2-616	4	$CONHSO_2$	NH	Z-9
2-617	4	$CONHSO_2$	NH	Z-10
2-618	4	$CONHSO_2$	NH	Z-11
2-619	4	$CONHSO_2$	NH	Z-12
2-620	4	$CONHSO_2$	NH	3-Py
2-621	4	$CONHSO_2$	NH	4-Py

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1159	4	$CONHSO_2$		Pyr
2-1160	4	$CONHSO_2$		Pipri
2-1161	4	$CONHSO_2$		Pipra
2-1162	4	$CONHSO_2$		Mor
2-1163	4	$CONHSO_2$		Thmor
2-1164	4	$CONHSO_2$		NHPyr
2-1165	4	$CONHSO_2$		NHPipri
2-1166	4	$CONHSO_2$		NHPipra

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1167	4	$CONHSO_2$	NHMor	
2-1168	4	$CONHSO_2$	NHThmor	

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1264	4	$CONHSO_2$	Thiad	
2-1265	4	$CONHSO_2$	NHThiad	

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1756	5	$CONHSO_2$	—	H
2-1757	5	$CONHSO_2$	—	Ph
2-1758	5	$CONHSO_2$	—	2-Me-Ph
2-1759	5	$CONHSO_2$	—	4-Me-Ph
2-1760	5	$CONHSO_2$	—	2,4-diMe-Ph
2-1761	5	$CONHSO_2$	—	3,4-diMe-Ph
2-1762	5	$CONHSO_2$	—	2-(CF_3)Ph
2-1763	5	$CONHSO_2$	—	4-(CF_3)Ph
2-1764	5	$CONHSO_2$	—	2-MeOPh
2-1765	5	$CONHSO_2$	—	4-MeOPh
2-1766	5	$CONHSO_2$	—	2-EtOPh
2-1767	5	$CONHSO_2$	—	4-EtOPh
2-1768	5	$CONHSO_2$	—	2-HOPh
2-1769	5	$CONHSO_2$	—	4-HOPh
2-1770	5	$CONHSO_2$	—	2-(HOOC)Ph
2-1771	5	$CONHSO_2$	—	4-(HOOC)Ph
2-1772	5	$CONHSO_2$	—	2-(MeOOC)Ph
2-1773	5	$CONHSO_2$	—	4-(MeOOC)Ph

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1774	5	$CONHSO_2$	—	2-(EtOOC)Ph
2-1775	5	$CONHSO_2$	—	4-(EtOOC)Ph
2-1776	5	$CONHSO_2$	—	2-(*t*BuOOC)Ph
2-1777	5	$CONHSO_2$	—	4-(*t*BuOOC)Ph
2-1778	5	$CONHSO_2$	—	2-Cl-Ph
2-1779	5	$CONHSO_2$	—	4-Cl-Ph
2-1780	5	$CONHSO_2$	—	2-Br-Ph
2-1781	5	$CONHSO_2$	—	4-Br-Ph
2-1782	5	$CONHSO_2$	—	2-I-Ph
2-1783	5	$CONHSO_2$	—	4-I-Ph
2-1784	5	$CONHSO_2$	—	2-NO_2-Ph
2-1785	5	$CONHSO_2$	—	4-NO_2-Ph
2-1786	5	$CONHSO_2$	—	2-NH_2-Ph
2-1787	5	$CONHSO_2$	—	4-NH_2-Ph
2-1788	5	$CONHSO_2$	—	2-(HO_3S)Ph
2-1789	5	$CONHSO_2$	—	4-(HO_3S)Ph
2-1790	5	$CONHSO_2$	—	2-(NH_2O_2S)Ph
2-1791	5	$CONHSO_2$	—	4-(NH_2O_2S)Ph
2-1792	5	$CONHSO_2$	—	2-CN-Ph
2-1793	5	$CONHSO_2$	—	4-CN-Ph
2-1794	5	$CONHSO_2$	—	2-($HOCH_2$)Ph
2-1795	5	$CONHSO_2$	—	4-($HOCH_2$)Ph
2-1796	5	$CONHSO_2$	—	Me
2-1797	5	$CONHSO_2$	—	Et

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1798	5	$CONHSO_2$	—	Pr
2-1799	5	$CONHSO_2$	—	*i*Pr
2-1800	5	$CONHSO_2$	—	Bu
2-1801	5	$CONHSO_2$	—	$HOOCCH_2$-
2-1802	5	$CONHSO_2$	—	$MeOOCCH_2$-
2-1803	5	$CONHSO_2$	—	MeCH(COOH)
2-1804	5	$CONHSO_2$	—	$HOOC-(CH_2)_2$-
2-1805	5	$CONHSO_2$	—	MeCH(COOMe)
2-1806	5	$CONHSO_2$	—	1-HOOC-*i*Bu
2-1807	5	$CONHSO_2$	—	1-MeOOC-*i*Bu
2-1808	5	$CONHSO_2$	—	1-HOOC-*i*Pn
2-1809	5	$CONHSO_2$	—	1-MeOOC-*i*Pn
2-1810	5	$CONHSO_2$	—	1-HOOC-2-Me-Bu
2-1811	5	$CONHSO_2$	—	1-MeOOC-2-Me-Bu
2-1812	5	$CONHSO_2$	—	$CH_2CH_2SO_3H$
2-1813	5	$CONHSO_2$	—	OH
2-1814	5	$CONHSO_2$	—	MeO
2-1815	5	$CONHSO_2$	—	EtO
2-1816	5	$CONHSO_2$	—	PrO
2-1817	5	$CONHSO_2$	—	*i*PrO
2-1818	5	$CONHSO_2$	—	BuO
2-1819	5	$CONHSO_2$	—	*i*BuO
2-1820	5	$CONHSO_2$	—	*s*BuO
2-1821	5	$CONHSO_2$	—	*t*BuO

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1822	5	$CONHSO_2$	—	HxO
2-1823	5	$CONHSO_2$	—	PhO
2-1824	5	$CONHSO_2$	—	BnO
2-1825	5	$CONHSO_2$	—	Z-1
2-1826	5	$CONHSO_2$	—	Z-2
2-1827	5	$CONHSO_2$	—	Z-3
2-1828	5	$CONHSO_2$	—	Z-4
2-1829	5	$CONHSO_2$	—	Z-5
2-1830	5	$CONHSO_2$	—	Z-6
2-1831	5	$CONHSO_2$	—	Z-7
2-1832	5	$CONHSO_2$	—	Z-8
2-1833	5	$CONHSO_2$	—	Z-9
2-1834	5	$CONHSO_2$	—	Z-10
2-1835	5	$CONHSO_2$	—	Z-11
2-1836	5	$CONHSO_2$	—	Z-12
2-1837	5	$CONHSO_2$	—	3-Py
2-1838	5	$CONHSO_2$	—	4-Py
2-1839	5	$CONHSO_2$	NH	H
2-1840	5	$CONHSO_2$	NH	Ph
2-1841	5	$CONHSO_2$	NH	2-Me-Ph
2-1842	5	$CONHSO_2$	NH	4-Me-Ph
2-1843	5	$CONHSO_2$	NH	2,4-diMe-Ph
2-1844	5	$CONHSO_2$	NH	3,4-diMe-Ph
2-1845	5	$CONHSO_2$	NH	2-(CF_3)Ph

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1846	5	$CONHSO_2$	NH	4-(CF_3)Ph
2-1847	5	$CONHSO_2$	NH	2-MeOPh
2-1848	5	$CONHSO_2$	NH	4-MeOPh
2-1849	5	$CONHSO_2$	NH	2-EtOPh
2-1850	5	$CONHSO_2$	NH	4-EtOPh
2-1851	5	$CONHSO_2$	NH	2-HOPh
2-1852	5	$CONHSO_2$	NH	4-HOPh
2-1853	5	$CONHSO_2$	NH	2-(HOOC)Ph
2-1854	5	$CONHSO_2$	NH	4-(HOOC)Ph
2-1855	5	$CONHSO_2$	NH	2-(MeOOC)Ph
2-1856	5	$CONHSO_2$	NH	4-(MeOOC)Ph
2-1857	5	$CONHSO_2$	NH	2-(EtOOC)Ph
2-1858	5	$CONHSO_2$	NH	4-(EtOOC)Ph
2-1859	5	$CONHSO_2$	NH	2-(*t*BuOOC)Ph
2-1860	5	$CONHSO_2$	NH	4-(*t*BuOOC)Ph
2-1861	5	$CONHSO_2$	NH	2-Cl-Ph
2-1862	5	$CONHSO_2$	NH	4-Cl-Ph
2-1863	5	$CONHSO_2$	NH	2-Br-Ph
2-1864	5	$CONHSO_2$	NH	4-Br-Ph
2-1865	5	$CONHSO_2$	NH	2-I-Ph
2-1866	5	$CONHSO_2$	NH	4-I-Ph
2-1867	5	$CONHSO_2$	NH	2-NO_2-Ph
2-1868	5	$CONHSO_2$	NH	4-NO_2-Ph
2-1869	5	$CONHSO_2$	NH	2-NH_2-Ph

Table 2 (cont.)

Cpd. No.	k	A	B	R1
2-1870	5	$CONHSO_2$	NH	4-NH_2-Ph
2-1871	5	$CONHSO_2$	NH	2-(HO_3S)Ph
2-1872	5	$CONHSO_2$	NH	4-(HO_3S)Ph
2-1873	5	$CONHSO_2$	NH	2-(NH_2O_2S)Ph
2-1874	5	$CONHSO_2$	NH	4-(NH_2O_2S)Ph
2-1875	5	$CONHSO_2$	NH	2-CN-Ph
2-1876	5	$CONHSO_2$	NH	4-CN-Ph
2-1877	5	$CONHSO_2$	NH	2-($HOCH_2$)Ph
2-1878	5	$CONHSO_2$	NH	4-($HOCH_2$)Ph
2-1879	5	$CONHSO_2$	NH	Me
2-1880	5	$CONHSO_2$	NH	Et
2-1881	5	$CONHSO_2$	NH	Pr
2-1882	5	$CONHSO_2$	NH	*i*Pr
2-1883	5	$CONHSO_2$	NH	Bu
2-1884	5	$CONHSO_2$	NH	$HOOCCH_2$-
2-1885	5	$CONHSO_2$	NH	$MeOOCCH_2$-
2-1886	5	$CONHSO_2$	NH	MeCH(COOH)
2-1887	5	$CONHSO_2$	NH	HOOC-$(CH_2)_2$-
2-1888	5	$CONHSO_2$	NH	MeCH(COOMe)
2-1889	5	$CONHSO_2$	NH	1-HOOC-*i*Bu
2-1890	5	$CONHSO_2$	NH	1-MeOOC-*i*Bu
2-1891	5	$CONHSO_2$	NH	1-HOOC-*i*Pn
2-1892	5	$CONHSO_2$	NH	1-MeOOC-*i*Pn
2-1893	5	$CONHSO_2$	NH	1-HOOC-2-Me-Bu

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1894	5	$CONHSO_2$	NH	1-MeOOC-2-Me-Bu
2-1895	5	$CONHSO_2$	NH	$CH_2CH_2SO_3H$
2-1896	5	$CONHSO_2$	NH	OH
2-1897	5	$CONHSO_2$	NH	MeO
2-1898	5	$CONHSO_2$	NH	EtO
2-1899	5	$CONHSO_2$	NH	PrO
2-1900	5	$CONHSO_2$	NH	*i*PrO
2-1901	5	$CONHSO_2$	NH	BuO
2-1902	5	$CONHSO_2$	NH	*i*BuO
2-1903	5	$CONHSO_2$	NH	*s*BuO
2-1904	5	$CONHSO_2$	NH	*t*BuO
2-1905	5	$CONHSO_2$	NH	HxO
2-1906	5	$CONHSO_2$	NH	PhO
2-1907	5	$CONHSO_2$	NH	BnO
2-1908	5	$CONHSO_2$	NH	Z-1
2-1909	5	$CONHSO_2$	NH	Z-2
2-1910	5	$CONHSO_2$	NH	Z-3
2-1911	5	$CONHSO_2$	NH	Z-4
2-1912	5	$CONHSO_2$	NH	Z-5
2-1913	5	$CONHSO_2$	NH	Z-6
2-1914	5	$CONHSO_2$	NH	Z-7
2-1915	5	$CONHSO_2$	NH	Z-8
2-1916	5	$CONHSO_2$	NH	Z-9
2-1917	5	$CONHSO_2$	NH	Z-10

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-1918	5	$CONHSO_2$	NH	Z-11
2-1919	5	$CONHSO_2$	NH	Z-12
2-1920	5	$CONHSO_2$	NH	3-Py
2-1921	5	$CONHSO_2$	NH	4-Py

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-2459	5	$CONHSO_2$	Pyr	
2-2460	5	$CONHSO_2$	Pipri	
2-2461	5	$CONHSO_2$	Pipra	
2-2462	5	$CONHSO_2$	Mor	
2-2463	5	$CONHSO_2$	Thmor	

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-2464	5	$CONHSO_2$	NHPyr	
2-2465	5	$CONHSO_2$	NHPipri	
2-2466	5	$CONHSO_2$	NHPipra	
2-2467	5	$CONHSO_2$	NHMor	
2-2468	5	$CONHSO_2$	NHThmor	

Table 2 (cont.)

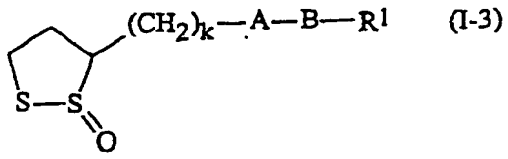
Cpd. No.	k	A	B	R^1
2-2564	5	$CONHSO_2$	Thiad	
2-2565	5	$CONHSO_2$	NHThiad	

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-2672	4	$CONMeSO_2$	—	Me

Table 2 (cont.)

Cpd. No.	k	A	B	R^1
2-2673	5	$CONMeSO_2$	—	Me



(I-3)

Table 3

Cpd. No.	k	A	B	R^1
3-456	4	$CONHSO_2$	—	H
3-457	4	$CONHSO_2$	—	Ph
3-458	4	$CONHSO_2$	—	2-Me-Ph

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-459	4	$CONHSO_2$	—	4-Me-Ph
3-460	4	$CONHSO_2$	—	2,4-diMe-Ph
3-461	4	$CONHSO_2$	—	3,4-diMe-Ph
3-462	4	$CONHSO_2$	—	2-(CF_3)Ph
3-463	4	$CONHSO_2$	—	4-(CF_3)Ph
3-464	4	$CONHSO_2$	—	2-MeOPh
3-465	4	$CONHSO_2$	—	4-MeOPh
3-466	4	$CONHSO_2$	—	2-EtOPh
3-467	4	$CONHSO_2$	—	4-EtOPh
3-468	4	$CONHSO_2$	—	2-HOPh
3-469	4	$CONHSO_2$	—	4-HOPh
3-470	4	$CONHSO_2$	—	2-(HOOC)Ph
3-471	4	$CONHSO_2$	—	4-(HOOC)Ph
3-472	4	$CONHSO_2$	—	2-(MeOOC)Ph
3-473	4	$CONHSO_2$	—	4-(MeOOC)Ph
3-474	4	$CONHSO_2$	—	2-(EtOOC)Ph
3-475	4	$CONHSO_2$	—	4-(EtOOC)Ph
3-476	4	$CONHSO_2$	—	2-(*t*BuOOC)Ph
3-477	4	$CONHSO_2$	—	4-(*t*BuOOC)Ph
3-478	4	$CONHSO_2$	—	2-Cl-Ph
3-479	4	$CONHSO_2$	—	4-Cl-Ph
3-480	4	$CONHSO_2$	—	2-Br-Ph
3-481	4	$CONHSO_2$	—	4-Br-Ph
3-482	4	$CONHSO_2$	—	2-I-Ph
3-483	4	$CONHSO_2$	—	4-I-Ph

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-484	4	$CONHSO_2$	—	2-NO_2-Ph
3-485	4	$CONHSO_2$	—	4-NO_2-Ph
3-486	4	$CONHSO_2$	—	2-NH_2-Ph
3-487	4	$CONHSO_2$	—	4-NH_2-Ph
3-488	4	$CONHSO_2$	—	2-(HO_3S)Ph
3-489	4	$CONHSO_2$	—	4-(HO_3S)Ph
3-490	4	$CONHSO_2$	—	2-(NH_2O_2S)Ph
3-491	4	$CONHSO_2$	—	4-(NH_2O_2S)Ph
3-492	4	$CONHSO_2$	—	2-CN-Ph
3-493	4	$CONHSO_2$	—	4-CN-Ph
3-494	4	$CONHSO_2$	—	2-($HOCH_2$)Ph
3-495	4	$CONHSO_2$	—	4-($HOCH_2$)Ph
3-496	4	$CONHSO_2$	—	Me
3-497	4	$CONHSO_2$	—	Et
3-498	4	$CONHSO_2$	—	Pr
3-499	4	$CONHSO_2$	—	*i*Pr
3-500	4	$CONHSO_2$	—	Bu
3-501	4	$CONHSO_2$	—	$HOOCCH_2$-
3-502	4	$CONHSO_2$	—	$MeOOCCH_2$-
3-503	4	$CONHSO_2$	—	MeCH(COOH)
3-504	4	$CONHSO_2$	—	HOOC-$(CH_2)_2$-
3-505	4	$CONHSO_2$	—	MeCH(COOMe)
3-506	4	$CONHSO_2$	—	1-HOOC-*i*Bu
3-507	4	$CONHSO_2$	—	1-MeOOC-*i*Bu
3-508	4	$CONHSO_2$	—	1-HOOC-*i*Pn

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-509	4	$CONHSO_2$	—	1-MeOOC-*i*Pn
3-510	4	$CONHSO_2$	—	1-HOOC-2-Me-Bu
3-511	4	$CONHSO_2$	—	1-MeOOC-2-Me-Bu
3-512	4	$CONHSO_2$	—	$CH_2CH_2SO_3H$
3-513	4	$CONHSO_2$	—	OH
3-514	4	$CONHSO_2$	—	MeO
3-515	4	$CONHSO_2$	—	EtO
3-516	4	$CONHSO_2$	—	PrO
3-517	4	$CONHSO_2$	—	*i*PrO
3-518	4	$CONHSO_2$	—	BuO
3-519	4	$CONHSO_2$	—	*i*BuO
3-520	4	$CONHSO_2$	—	*s*BuO
3-521	4	$CONHSO_2$	—	*t*BuO
3-522	4	$CONHSO_2$	—	HxO
3-523	4	$CONHSO_2$	—	PhO
3-524	4	$CONHSO_2$	—	BnO
3-525	4	$CONHSO_2$	—	Z-1
3-526	4	$CONHSO_2$	—	Z-2
3-527	4	$CONHSO_2$	—	Z-3
3-528	4	$CONHSO_2$	—	Z-4
3-529	4	$CONHSO_2$	—	Z-5
3-530	4	$CONHSO_2$	—	Z-6
3-531	4	$CONHSO_2$	—	Z-7
3-532	4	$CONHSO_2$	—	Z-8
3-533	4	$CONHSO_2$	—	Z-9

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-534	4	$CONHSO_2$	—	Z-10
3-535	4	$CONHSO_2$	—	Z-11
3-536	4	$CONHSO_2$	—	Z-12
3-537	4	$CONHSO_2$	—	3-Py
3-538	4	$CONHSO_2$	—	4-Py
3-539	4	$CONHSO_2$	NH	H
3-540	4	$CONHSO_2$	NH	Ph
3-541	4	$CONHSO_2$	NH	2-Me-Ph
3-542	4	$CONHSO_2$	NH	4-Me-Ph
3-543	4	$CONHSO_2$	NH	2.4-diMe-Ph
3-544	4	$CONHSO_2$	NH	3.4-diMe-Ph
3-545	4	$CONHSO_2$	NH	2-(CF_3)Ph
3-546	4	$CONHSO_2$	NH	4-(CF_3)Ph
3-547	4	$CONHSO_2$	NH	2-MeOPh
3-548	4	$CONHSO_2$	NH	4-MeOPh
3-549	4	$CONHSO_2$	NH	2-EtOPh
3-550	4	$CONHSO_2$	NH	4-EtOPh
3-551	4	$CONHSO_2$	NH	2-HOPh
3-552	4	$CONHSO_2$	NH	4-HOPh
3-553	4	$CONHSO_2$	NH	2-(HOOC)Ph
3-554	4	$CONHSO_2$	NH	4-(HOOC)Ph
3-555	4	$CONHSO_2$	NH	2-(MeOOC)Ph
3-556	4	$CONHSO_2$	NH	4-(MeOOC)Ph
3-557	4	$CONHSO_2$	NH	2-(EtOOC)Ph
3-558	4	$CONHSO_2$	NH	4-(EtOOC)Ph

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-559	4	$CONHSO_2$	NH	2-(*t*BuOOC)Ph
3-560	4	$CONHSO_2$	NH	4-(*t*BuOOC)Ph
3-561	4	$CONHSO_2$	NH	2-Cl-Ph
3-562	4	$CONHSO_2$	NH	4-Cl-Ph
3-563	4	$CONHSO_2$	NH	2-Br-Ph
3-564	4	$CONHSO_2$	NH	4-Br-Ph
3-565	4	$CONHSO_2$	NH	2-I-Ph
3-566	4	$CONHSO_2$	NH	4-I-Ph
3-567	4	$CONHSO_2$	NH	2-NO_2-Ph
3-568	4	$CONHSO_2$	NH	4-NO_2-Ph
3-569	4	$CONHSO_2$	NH	2-NH_2-Ph
3-570	4	$CONHSO_2$	NH	4-NH_2-Ph
3-571	4	$CONHSO_2$	NH	2-(HO_3S)Ph
3-572	4	$CONHSO_2$	NH	4-(HO_3S)Ph
3-573	4	$CONHSO_2$	NH	2-(NH_2O_2S)Ph
3-574	4	$CONHSO_2$	NH	4-(NH_2O_2S)Ph
3-575	4	$CONHSO_2$	NH	2-CN-Ph
3-576	4	$CONHSO_2$	NH	4-CN-Ph
3-577	4	$CONHSO_2$	NH	2-($HOCH_2$)Ph
3-578	4	$CONHSO_2$	NH	4-($HOCH_2$)Ph
3-579	4	$CONHSO_2$	NH	Me
3-580	4	$CONHSO_2$	NH	Et
3-581	4	$CONHSO_2$	NH	Pr
3-582	4	$CONHSO_2$	NH	*i*Pr
3-583	4	$CONHSO_2$	NH	Bu

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-584	4	$CONHSO_2$	NH	$HOOCCH_2$-
3-585	4	$CONHSO_2$	NH	$MeOOCCH_2$-
3-586	4	$CONHSO_2$	NH	MeCH(COOH)
3-587	4	$CONHSO_2$	NH	HOOC-$(CH_2)_2$-
3-588	4	$CONHSO_2$	NH	MeCH(COOMe)
3-589	4	$CONHSO_2$	NH	1-HOOC-*i*Bu
3-590	4	$CONHSO_2$	NH	1-MeOOC-*i*Bu
3-591	4	$CONHSO_2$	NH	1-HOOC-*i*Pn
3-592	4	$CONHSO_2$	NH	1-MeOOC-*i*Pn
3-593	4	$CONHSO_2$	NH	1-HOOC-2-Me-Bu
3-594	4	$CONHSO_2$	NH	1-MeOOC-2-Me-Bu
3-595	4	$CONHSO_2$	NH	$CH_2CH_2SO_3H$
3-596	4	$CONHSO_2$	NH	OH
3-597	4	$CONHSO_2$	NH	MeO
3-598	4	$CONHSO_2$	NH	EtO
3-599	4	$CONHSO_2$	NH	PrO
3-600	4	$CONHSO_2$	NH	*i*PrO
3-601	4	$CONHSO_2$	NH	BuO
3-602	4	$CONHSO_2$	NH	*i*BuO
3-603	4	$CONHSO_2$	NH	*s*BuO
3-604	4	$CONHSO_2$	NH	*t*BuO
3-605	4	$CONHSO_2$	NH	HxO
3-606	4	$CONHSO_2$	NH	PhO
3-607	4	$CONHSO_2$	NH	BnO
3-608	4	$CONHSO_2$	NH	Z-1

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-609	4	$CONHSO_2$	NH	Z-2
3-610	4	$CONHSO_2$	NH	Z-3
3-611	4	$CONHSO_2$	NH	Z-4
3-612	4	$CONHSO_2$	NH	Z-5
3-613	4	$CONHSO_2$	NH	Z-6
3-614	4	$CONHSO_2$	NH	Z-7
3-615	4	$CONHSO_2$	NH	Z-8
3-616	4	$CONHSO_2$	NH	Z-9
3-617	4	$CONHSO_2$	NH	Z-10
3-618	4	$CONHSO_2$	NH	Z-11
3-619	4	$CONHSO_2$	NH	Z-12
3-620	4	$CONHSO_2$	NH	3-Py
3-621	4	$CONHSO_2$	NH	4-Py

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1159	4	$CONHSO_2$		Pyr
3-1160	4	$CONHSO_2$		Pipri
3-1161	4	$CONHSO_2$		Pipra
3-1162	4	$CONHSO_2$		Mor
3-1163	4	$CONHSO_2$		Thmor
3-1164	4	$CONHSO_2$		NHPyr
3-1165	4	$CONHSO_2$		NHPipri
3-1166	4	$CONHSO_2$		NHPipra

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1167	4	$CONHSO_2$		NHMor
3-1168	4	$CONHSO_2$		NHThmor

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1264	4	$CONHSO_2$	Thiad	
3-1265	4	$CONHSO_2$	NHThiad	

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1756	5	$CONHSO_2$	—	H
3-1757	5	$CONHSO_2$	—	Ph
3-1758	5	$CONHSO_2$	—	2-Me-Ph
3-1759	5	$CONHSO_2$	—	4-Me-Ph
3-1760	5	$CONHSO_2$	—	2,4-diMe-Ph
3-1761	5	$CONHSO_2$	—	3,4-diMe-Ph
3-1762	5	$CONHSO_2$	—	2-(CF_3)Ph
3-1763	5	$CONHSO_2$	—	4-(CF_3)Ph
3-1764	5	$CONHSO_2$	—	2-MeOPh
3-1765	5	$CONHSO_2$	—	4-MeOPh
3-1766	5	$CONHSO_2$	—	2-EtOPh
3-1767	5	$CONHSO_2$	—	4-EtOPh
3-1768	5	$CONHSO_2$	—	2-HOPh
3-1769	5	$CONHSO_2$	—	4-HOPh
3-1770	5	$CONHSO_2$	—	2-(HOOC)Ph
3-1771	5	$CONHSO_2$	—	4-(HOOC)Ph
3-1772	5	$CONHSO_2$	—	2-(MeOOC)Ph
3-1773	5	$CONHSO_2$	—	4-(MeOOC)Ph

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1774	5	$CONHSO_2$	—	2-(EtOOC)Ph
3-1775	5	$CONHSO_2$	—	4-(EtOOC)Ph
3-1776	5	$CONHSO_2$	—	2-(*t*BuOOC)Ph
3-1777	5	$CONHSO_2$	—	4-(*t*BuOOC)Ph
3-1778	5	$CONHSO_2$	—	2-Cl-Ph
3-1779	5	$CONHSO_2$	—	4-Cl-Ph
3-1780	5	$CONHSO_2$	—	2-Br-Ph
3-1781	5	$CONHSO_2$	—	4-Br-Ph
3-1782	5	$CONHSO_2$	—	2-I-Ph
3-1783	5	$CONHSO_2$	—	4-I-Ph
3-1784	5	$CONHSO_2$	—	2-NO_2-Ph
3-1785	5	$CONHSO_2$	—	4-NO_2-Ph
3-1786	5	$CONHSO_2$	—	2-NH_2-Ph
3-1787	5	$CONHSO_2$	—	4-NH_2-Ph
3-1788	5	$CONHSO_2$	—	2-(HO_3S)Ph
3-1789	5	$CONHSO_2$	—	4-(HO_3S)Ph
3-1790	5	$CONHSO_2$	—	2-(NH_2O_2S)Ph
3-1791	5	$CONHSO_2$	—	4-(NH_2O_2S)Ph
3-1792	5	$CONHSO_2$	—	2-CN-Ph
3-1793	5	$CONHSO_2$	—	4-CN-Ph
3-1794	5	$CONHSO_2$	—	2-($HOCH_2$)Ph
3-1795	5	$CONHSO_2$	—	4-($HOCH_2$)Ph
3-1796	5	$CONHSO_2$	—	Me
3-1797	5	$CONHSO_2$	—	Et

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1798	5	$CONHSO_2$	—	Pr
3-1799	5	$CONHSO_2$	—	*i*Pr
3-1800	5	$CONHSO_2$	—	Bu
3-1801	5	$CONHSO_2$	—	$HOOCCH_2$-
3-1802	5	$CONHSO_2$	—	$MeOOCCH_2$-
3-1803	5	$CONHSO_2$	—	MeCH(COOH)
3-1804	5	$CONHSO_2$	—	$HOOC-(CH_2)_2$-
3-1805	5	$CONHSO_2$	—	MeCH(COOMe)
3-1806	5	$CONHSO_2$	—	1-HOOC-*i*Bu
3-1807	5	$CONHSO_2$	—	1-MeOOC-*i*Bu
3-1808	5	$CONHSO_2$	—	1-HOOC-*i*Pn
3-1809	5	$CONHSO_2$	—	1-MeOOC-*i*Pn
3-1810	5	$CONHSO_2$	—	1-HOOC-2-Me-Bu
3-1811	5	$CONHSO_2$	—	1-MeOOC-2-Me-Bu
3-1812	5	$CONHSO_2$	—	$CH_2CH_2SO_3H$
3-1813	5	$CONHSO_2$	—	OH
3-1814	5	$CONHSO_2$	—	MeO
3-1815	5	$CONHSO_2$	—	EtO
3-1816	5	$CONHSO_2$	—	PrO
3-1817	5	$CONHSO_2$	—	*i*PrO
3-1818	5	$CONHSO_2$	—	BuO
3-1819	5	$CONHSO_2$	—	*i*BuO
3-1820	5	$CONHSO_2$	—	*s*BuO
3-1821	5	$CONHSO_2$	—	*t*BuO

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1822	5	$CONHSO_2$	—	HxO
3-1823	5	$CONHSO_2$	—	PhO
3-1824	5	$CONHSO_2$	—	BnO
3-1825	5	$CONHSO_2$	—	Z-1
3-1826	5	$CONHSO_2$	—	Z-2
3-1827	5	$CONHSO_2$	—	Z-3
3-1828	5	$CONHSO_2$	—	Z-4
3-1829	5	$CONHSO_2$	—	Z-5
3-1830	5	$CONHSO_2$	—	Z-6
3-1831	5	$CONHSO_2$	—	Z-7
3-1832	5	$CONHSO_2$	—	Z-8
3-1833	5	$CONHSO_2$	—	Z-9
3-1834	5	$CONHSO_2$	—	Z-10
3-1835	5	$CONHSO_2$	—	Z-11
3-1836	5	$CONHSO_2$	—	Z-12
3-1837	5	$CONHSO_2$	—	3-Py
3-1838	5	$CONHSO_2$	—	4-Py
3-1839	5	$CONHSO_2$	NH	H
3-1840	5	$CONHSO_2$	NH	Ph
3-1841	5	$CONHSO_2$	NH	2-Me-Ph
3-1842	5	$CONHSO_2$	NH	4-Me-Ph
3-1843	5	$CONHSO_2$	NH	2,4-diMe-Ph
3-1844	5	$CONHSO_2$	NH	3,4-diMe-Ph
3-1845	5	$CONHSO_2$	NH	2-(CF_3)Ph

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1846	5	$CONHSO_2$	NH	4-(CF_3)Ph
3-1847	5	$CONHSO_2$	NH	2-MeOPh
3-1848	5	$CONHSO_2$	NH	4-MeOPh
3-1849	5	$CONHSO_2$	NH	2-EtOPh
3-1850	5	$CONHSO_2$	NH	4-EtOPh
3-1851	5	$CONHSO_2$	NH	2-HOPh
3-1852	5	$CONHSO_2$	NH	4-HOPh
3-1853	5	$CONHSO_2$	NH	2-(HOOC)Ph
3-1854	5	$CONHSO_2$	NH	4-(HOOC)Ph
3-1855	5	$CONHSO_2$	NH	2-(MeOOC)Ph
3-1856	5	$CONHSO_2$	NH	4-(MeOOC)Ph
3-1857	5	$CONHSO_2$	NH	2-(EtOOC)Ph
3-1858	5	$CONHSO_2$	NH	4-(EtOOC)Ph
3-1859	5	$CONHSO_2$	NH	2-(*t*BuOOC)Ph
3-1860	5	$CONHSO_2$	NH	4-(*t*BuOOC)Ph
3-1861	5	$CONHSO_2$	NH	2-Cl-Ph
3-1862	5	$CONHSO_2$	NH	4-Cl-Ph
3-1863	5	$CONHSO_2$	NH	2-Br-Ph
3-1864	5	$CONHSO_2$	NH	4-Br-Ph
3-1865	5	$CONHSO_2$	NH	2-I-Ph
3-1866	5	$CONHSO_2$	NH	4-I-Ph
3-1867	5	$CONHSO_2$	NH	2-NO_2-Ph
3-1868	5	$CONHSO_2$	NH	4-NO_2-Ph
3-1869	5	$CONHSO_2$	NH	2-NH_2-Ph

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1870	5	$CONHSO_2$	NH	4-NH_2-Ph
3-1871	5	$CONHSO_2$	NH	2-(HO_3S)Ph
3-1872	5	$CONHSO_2$	NH	4-(HO_3S)Ph
3-1873	5	$CONHSO_2$	NH	2-(NH_2O_2S)Ph
3-1874	5	$CONHSO_2$	NH	4-(NH_2O_2S)Ph
3-1875	5	$CONHSO_2$	NH	2-CN-Ph
3-1876	5	$CONHSO_2$	NH	4-CN-Ph
3-1877	5	$CONHSO_2$	NH	2-($HOCH_2$)Ph
3-1878	5	$CONHSO_2$	NH	4-($HOCH_2$)Ph
3-1879	5	$CONHSO_2$	NH	Me
3-1880	5	$CONHSO_2$	NH	Et
3-1881	5	$CONHSO_2$	NH	Pr
3-1882	5	$CONHSO_2$	NH	*i*Pr
3-1883	5	$CONHSO_2$	NH	Bu
3-1884	5	$CONHSO_2$	NH	$HOOCCH_2$-
3-1885	5	$CONHSO_2$	NH	$MeOOCCH_2$-
3-1886	5	$CONHSO_2$	NH	MeCH(COOH)
3-1887	5	$CONHSO_2$	NH	HOOC-$(CH_2)_2$-
3-1888	5	$CONHSO_2$	NH	MeCH(COOMe)
3-1889	5	$CONHSO_2$	NH	1-HOOC-*i*Bu
3-1890	5	$CONHSO_2$	NH	1-MeOOC-*i*Bu
3-1891	5	$CONHSO_2$	NH	1-HOOC-*i*Pn
3-1892	5	$CONHSO_2$	NH	1-MeOOC-*i*Pn
3-1893	5	$CONHSO_2$	NH	1-HOOC-2-Me-Bu

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1894	5	$CONHSO_2$	NH	1-MeOOC-2-Me-Bu
3-1895	5	$CONHSO_2$	NH	$CH_2CH_2SO_3H$
3-1896	5	$CONHSO_2$	NH	OH
3-1897	5	$CONHSO_2$	NH	MeO
3-1898	5	$CONHSO_2$	NH	EtO
3-1899	5	$CONHSO_2$	NH	PrO
3-1900	5	$CONHSO_2$	NH	*i*PrO
3-1901	5	$CONHSO_2$	NH	BuO
3-1902	5	$CONHSO_2$	NH	*i*BuO
3-1903	5	$CONHSO_2$	NH	*s*BuO
3-1904	5	$CONHSO_2$	NH	*t*BuO
3-1905	5	$CONHSO_2$	NH	HxO
3-1906	5	$CONHSO_2$	NH	PhO
3-1907	5	$CONHSO_2$	NH	BnO
3-1908	5	$CONHSO_2$	NH	Z-1
3-1909	5	$CONHSO_2$	NH	Z-2
3-1910	5	$CONHSO_2$	NH	Z-3
3-1911	5	$CONHSO_2$	NH	Z-4
3-1912	5	$CONHSO_2$	NH	Z-5
3-1913	5	$CONHSO_2$	NH	Z-6
3-1914	5	$CONHSO_2$	NH	Z-7
3-1915	5	$CONHSO_2$	NH	Z-8
3-1916	5	$CONHSO_2$	NH	Z-9
3-1917	5	$CONHSO_2$	NH	Z-10

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-1918	5	$CONHSO_2$	NH	Z-11
3-1919	5	$CONHSO_2$	NH	Z-12
3-1920	5	$CONHSO_2$	NH	3-Py
3-1921	5	$CONHSO_2$	NH	4-Py

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-2459	5	$CONHSO_2$	Pyr	
3-2460	5	$CONHSO_2$	Pipri	
3-2461	5	$CONHSO_2$	Pipra	
3-2462	5	$CONHSO_2$	Mor	
3-2463	5	$CONHSO_2$	Thmor	

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-2464	5	$CONHSO_2$		NHPyr
3-2465	5	$CONHSO_2$		NHPipri
3-2466	5	$CONHSO_2$		NHPipra
3-2467	5	$CONHSO_2$		NHMor
3-2468	5	$CONHSO_2$		NHThmor

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-2564	5	$CONHSO_2$		Thiad
3-2565	5	$CONHSO_2$		NHThiad

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-2672	4	$CONMeSO_2$	—	Me

Table 3 (cont.)

Cpd. No.	k	A	B	R^1
3-2673	5	$CONMeSO_2$	—	Me

[0063] Of the above compounds, preferred compounds are Compounds No.: 1-456, 1-457, 1-458, 1-459, 1-460, 1-461, 1-462, 1-463, 1-464, 1-465, 1-466, 1-467, 1-468, 1-469, 1-470, 1-471, 1-472, 1-473, 1-474, 1-475, 1-476, 1-477, 1-478, 1-479, 1-480, 1-481, 1-482, 1-483, 1-484, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-396, 1-494, 1-495, 1-496, 1-497, 1-498, 1-499, 1-500, 1-501, 1-502, 1-503, 1-504, 1-505, 1-506, 1-507, 1-508, 1-509, 1-510, 1-511, 1-512, 1-513, 1-514, 1-515, 1-516, 1-517, 1-518, 1-519, 1-520, 1-521, 1-522, 1-523, 1-524, 1-525, 1-526, 1-527, 1-528, 1-529, 1-530, 1-531, 1-532, 1-533, 1-534, 1-535, 1-536, 1-537, 1-538, 1-539, 1-540, 1-541, 1-542, 1-543, 1-544, 1-545, 1-546, 1-547, 1-548, 1-549, 1-550, 1-551, 1-552, 1-553, 1-554, 1-555, 1-556, 1-557, 1-558, 1-559, 1-560, 1-561, 1-562, 1-563, 1-564; 1-565, 1-566, 1-567, 1-568, 1-569, 1-570, 1-571, 1-572, 1-573, 1-574, 1-575, 1-576, 1-577, 1-578, 1-579, 1-580, 1-581, 1-582, 1-583, 1-584, 1-585, 1-586, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-593, 1-594, 1-595, 1-596, 1-597, 1-598, 1-599, 1-600, 1-601, 1-602, 1-603, 1-604, 1-605, 1-606, 1-607, 1-608, 1-609, 1-610, 1-611, 1-612, 1-613, 1-614, 1-615, 1-616, 1-617, 1-618, 1-619, 1-620, 1-621, 1-1159, 1-1160, 1-1161, 1-1162, 1-1163, 1-1164, 1-1165, 1-1166, 1-1167, 1-1168, 1-1264, 1-1265, 1-1756, 1-1757, 1-1758, 1-1759, 1-1760, 1-1761, 1-1762, 1-1763, 1-764, 1-1765, 1-1766, 1-1767, 1-1768, 1-1769, 1-1770, 1-1771, 1-1772, 1-1773, 1-1774, 1-1775, 1-1776, 1-1777, 1-1778, 1-1779, 1-1780, 1-1781, 1-1782, 1-1783, 1-1784, 1-1785, 1-1786, 1-1787, 1-1788, 1-1789, 1-1790, 1-1791, 1-1792, 1-1793, 1-1794, 1-1795, 1-1796, 1-1797, 1-1798, 1-1799, 1-1800, 1-1801, 1-1802, 1-1803, 1-1804, 1-1805, 1-1806, 1-1807, 1-1808, 1-1809, 1-1810, 1-1811, 1-1812, 1-1813, 1-1814, 1-1815, 1-1816, 1-1817, 1-1818, 1-1819, 1-1820, 1-1821, 1-1822, 1-1823, 1-1824, 1-1825, 1-1826, 1-1827, 1-1828, 1-1829, 1-1830, 1-1831, 1-1832, 1-1833, 1-1834, 1-1835, 1-1836, 1-1837, 1-1838, 1-1839, 1-1840, 1-1841, 1-1842, 1-1843, 1-1844, 1-1845, 1-1846, 1-1847, 1-1848, 1-1849, 1-1850, 1-1851, 1-1852, 1-1853, 1-1854, 1-1855, 1-1856, 1-1857, 1-1858, 1-1859, 1-1860, 1-1861, 1-1862, 1-1863, 1-1864, 1-1865, 1-1866, 1-1867, 1-1868, 1-1869, 1-1870, 1-1871, 1-1872, 1-1873, 1-1874, 1-1875, 1-1876, 1-1877, 1-1878, 1-1879, 1-1880, 1-1881, 1-1882, 1-1883, 1-1884, 1-1885, 1-1886, 1-1887, 1-1888, 1-1889, 1-1890, 1-1891, 1-1892, 1-1893, 1-1894, 1-1895, 1-1896, 1-1897, 1-1898, 1-1899, 1-1900, 1-1901, 1-1902, 1-1903, 1-1904, 1-1905, 1-1906, 1-1907, 1-1908, 1-1909, 1-1910, 1-1911, 1-1912, 1-1913, 1-1914, 1-1915, 1-1916, 1-1917, 1-1918, 1-1919, 1-1920, 1-1921, 1-2459, 1-2460, 1-2461, 1-2462, 1-2463, 1-2464, 1-2465, 1-2466, 1-2467, 1-2468, 1-2564, 1-2565, 2-456, 2-457, 2-458, 2-459, 2-460, 2-461, 2-462, 2-463, 2-464, 2-465, 2-466, 2-467, 2-468, 2-469, 2-470, 2-471, 2-472, 2-473, 2-474, 2-475, 2-476, 2-477, 2-478, 2-479, 2-480, 2-481, 2-482, 2-483, 2-484, 2-485, 2-486, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-493, 2-494, 2-495, 2-496, 2-497, 2-498, 2-499, 2-500, 2-501, 2-502, 2-503, 2-504, 2-505, 2-506, 2-507, 2-508, 2-509, 2-510, 2-511, 2-512, 2-513, 2-514, 2-515, 2-516, 2-517, 2-518, 2-519, 2-520, 2-521, 2-522, 2-523, 2-524, 2-525, 2-526, 2-527, 2-528, 2-529, 2-530, 2-531, 2-532, 2-533, 2-534, 2-535, 2-536, 2-537, 2-538, 2-539, 2-540, 2-541, 2-542, 2-543, 2-544, 2-545, 2-546, 2-547, 2-548, 2-549, 2-550, 2-551, 2-552, 2-553, 2-554, 2-555, 2-556, 2-557, 2-558, 2-559, 2-560, 2-561, 2-562, 2-563, 2-564, 2-565, 2-566, 2-567, 2-568, 2-569, 2-570, 2-571, 2-572, 2-573, 2-574, 2-575, 2-576, 2-577, 2-578, 2-579, 2-580, 2-581, 2-582, 2-583, 2-584, 2-585, 2-586, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-593, 2-594, 2-595, 2-596, 2-597, 2-598, 2-599, 2-600, 2-601, 2-602, 2-603, 2-604, 2-605, 2-606, 2-607, 2-608, 2-609, 2-610, 2-611, 2-612, 2-613, 2-614, 2-615, 2-616, 2-617, 2-618, 2-619, 2-620, 2-621, 2-1159, 2-1160, 2-1161, 2-1162, 2-1163, 2-1164, 2-1165, 2-1166, 2-1167, 2-1168, 2-1264, 2-1265, 2-1756, 2-1757, 2-1758, 2-1759, 2-1760, 2-1761, 2-1762, 2-1763, 2-1764, 2-1765, 2-1766, 2-1767, 2-1768, 2-1769, 2-1770, 2-1771, 2-1772, 2-1773, 2-1774, 2-1775, 2-1776, 2-1777, 2-1778, 2-1779, 2-1780, 2-1781, 2-1782, 2-1783, 2-1784, 2-1785, 2-1786, 2-1787, 2-1788, 2-1789, 2-1790, 2-1791, 2-1792, 2-1793, 2-1794, 2-1795, 2-1796, 2-1797, 2-1798, 2-1799, 2-1800, 2-1801, 2-1802, 2-1803, 2-1804, 2-1805, 2-1806, 2-1807, 2-1808, 2-1809, 2-1810, 2-1811, 2-1812, 2-1813, 2-1814, 2-1815, 2-1816, 2-1817, 2-1818, 2-1819, 2-1820, 2-1821, 2-1822, 2-1823, 2-1824, 2-1825, 2-1826, 2-1827, 2-1828, 2-1829, 2-1830, 2-1831, 2-1832, 2-1833, 2-1834, 2-1835, 2-1836, 2-1837, 2-1838, 2-1839, 2-1840, 2-1841, 2-1842, 2-1843, 2-1844, 2-1845, 2-1846, 2-1847, 2-1848, 2-1849, 2-1850, 2-1851, 2-1852, 2-1853, 2-1854, 2-1855, 2-1856, 2-1857, 2-1858, 2-1859, 2-1860, 2-1861, 2-1862, 2-1863, 2-1864, 2-1865, 2-1866, 2-1867, 2-1868, 2-1869, 2-1870, 2-1871, 2-1872, 2-1873, 2-1874, 2-1875, 2-1876, 2-1877, 2-1878, 2-1879, 2-1880, 2-1881, 2-1882, 2-1883, 2-1884, 2-1885, 2-1886, 2-1887, 2-1888, 2-1889, 2-1890, 2-1891, 2-1892, 2-1893, 2-1894, 2-1895, 2-1896, 2-1897, 2-1898,

2-1899, 2-1900, 2-1901, 2-1902, 2-1903, 2-1904, 2-1905, 2-1906, 2-1907, 2-1908, 2-1909, 2-1910, 2-1911, 2-1912, 2-1913, 2-1914, 2-1915, 2-1916, 2-1917, 2-1918, 2-1919, 2-1920, 2-1921, 2-2459, 2-2460, 2-2461, 2-2462, 2-2463, 2-2464, 2-2465, 2-2466, 2-2467, 2-2468, 2-2564, 2-2565, 3-456, 3-457, 3-458, 3-459, 3-460, 3-461, 3-462, 3-463, 3-464, 3-465, 3-466, 3-467, 3-468, 3-469, 3-470, 3-471, 3-472, 3-473, 3-474, 3-475, 3-476, 3-477, 3-478, 3-479, 3-480, 3-481, 3-482, 3-483, 3-484, 3-485, 3-486, 3-487, 3-488, 3-489, 3-490, 3-491, 3-492, 3-493, 3-494, 3-495, 3-496, 3-497, 3-498, 3-499, 3-500, 3-501, 3-502, 3-503, 3-504, 3-505, 3-506, 3-507, 3-508, 3-509, 3-510, 3-511, 3-512, 3-513, 3-514, 3-515, 3-516, 3-517, 3-518, 3-519, 3-520, 3-521, 3-522, 3-523, 3-524, 3-525, 3-526, 3-527, 3-528, 3-529, 3-530, 3-531, 3-532, 3-533, 3-534, 3-535, 3-536, 3-537, 3-538, 3-539, 3-540, 3-541, 3-542, 3-543, 3-544, 3-545, 3-546, 3-547, 3-548, 3-549, 3-550, 3-551, 3-552, 3-553, 3-554, 3-555, 3-556, 3-557, 3-558, 3-559, 3-560, 3-561, 3-562, 3-563, 3-564, 3-565, 3-566, 3-567, 3-568, 3-569, 3-570, 3-571, 3-572, 3-573, 3-574, 3-575, 3-576, 3-577, 3-578, 3-579, 3-580, 3-581, 3-582, 3-583, 3-584, 3-585, 3-586, 3-587, 3-588, 3-589, 3-590, 3-591, 3-592, 3-593, 3-594, 3-595, 3-596, 3-597, 3-598, 3-599, 3-600, 3-601, 3-602, 3-603, 3-604, 3-605, 3-606, 3-607, 3-608, 3-609, 3-610, 3-611, 3-612, 3-613, 3-614, 3-615, 3-616, 3-617, 3-618, 3-619, 3-620, 3-621, 3-1159, 3-1160, 3-1161, 3-1162, 3-1163, 3-1164, 3-1165, 3-1166, 3-1167, 3-1168, 3-1264, 3-1265, 3-1756, 3-1757, 3-1758, 3-1759, 3-1760, 3-1761, 3-1762, 3-1763, 3-1764, 3-1765, 3-1766, 3-1767, 3-1768, 3-1769, 3-1770, 3-1771, 3-1772, 3-1773, 3-1774, 3-1775, 3-1776, 3-1777, 3-1778, 3-1779, 3-1780, 3-1781, 3-1782, 3-1783, 3-1784, 3-1785, 3-1786, 3-1787, 3-1788, 3-1789, 3-1790, 3-1791, 3-1792, 3-1793, 3-1794, 3-1795, 3-1796, 3-1797, 3-1798, 3-1799, 3-1800, 3-1801, 3-1802, 3-1803, 3-1804, 3-1805, 3-1806, 3-1807, 3-1808, 3-1809, 3-1810, 3-1811, 3-1812, 3-1813, 3-1814, 3-1815, 3-1816, 3-1817, 3-1818, 3-1819, 3-1820, 3-1821, 3-1822, 3-1823, 3-1824, 3-1825, 3-1826, 3-1827, 3-1828, 3-1829, 3-1830, 3-1831, 3-1832, 3-1833, 3-1834, 3-1835, 3-1836, 3-1837, 3-1838, 3-1839, 3-1840, 3-1841, 3-1842, 3-1843, 3-1844, 3-1845, 3-1846, 3-1847, 3-1848, 3-1849, 3-1850, 3-1851, 3-1852, 3-1853, 3-1854, 3-1855, 3-1856, 3-1857, 3-1858, 3-1859, 3-1860, 3-1861, 3-1862, 3-1863, 3-1864, 3-1865, 3-1866, 3-1867, 3-1868, 3-1869, 3-1870, 3-1871, 3-1872, 3-1873, 3-1874, 3-1875, 3-1876, 3-1877, 3-1878, 3-1879, 3-1880, 3-1881, 3-1882, 3-1883, 3-1884, 3-1885, 3-1886, 3-1887, 3-1888, 3-1889, 3-1890, 3-1891, 3-1892, 3-1893, 3-1894, 3-1895, 3-1896, 3-1897, 3-1898, 3-1899, 3-1900, 3-1901, 3-1902, 3-1903, 3-1904, 3-1905, 3-1906, 3-1907, 3-1908, 3-1909, 3-1910, 3-1911, 3-1912, 3-1913, 3-1914, 3-1915, 3-1916, 3-1917, 3-1918, 3-1919, 3-1920, 3-1921, 3-2459, 3-2460, 3-2461, 3-2462, 3-2463, 3-2464, 3-2465, 3-2466, 3-2467, 3-2468, 3-2564 and 3-2565.

[0064] The following compounds are more preferred, that is Compounds No.: 1-456, 1-457, 1-458, 1-459, 1-460, 1-461, 1-462, 1-463, 1-464, 1-465, 1-466, 1-467, 1-468, 1-469, 1-470, 1-471, 1-472, 1-473, 1-474, 1-475, 1-476, 1-477, 1-478, 1-479, 1-480, 1-481, 1-482, 1-483, 1-484, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-495, 1-496, 1-497, 1-498, 1-499, 1-500, 1-501, 1-502, 1-503, 1-504, 1-505, 1-506, 1-507, 1-508, 1-509, 1-510, 1-511, 1-512, 1-513, 1-514, 1-515, 1-516, 1-517, 1-518, 1-519, 1-520, 1-521, 1-522, 1-523, 1-524, 1-525, 1-526, 1-527, 1-528, 1-529, 1-530, 1-531, 1-532, 1-533, 1-534, 1-535, 1-536, 1-537, 1-538, 1-539, 1-2564 and 1-2565.

[0065] The following compounds are still more preferred, that is Compounds No.: 1-457, 1-458, 1-459, 1-460, 1-461, 1-462, 1-463, 1-464, 1-465, 1-466, 1-467, 1-468, 1-469, 1-470, 1-471, 1-472, 1-473, 1-474, 1-475, 1-476, 1-477, 1-478, 1-479, 1-480, 1-481, 1-482, 1-483, 1-484, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-495, 1-496, 1-497, 1-498, 1-499, 1-500, 1-501, 1-502, 1-503, 1-504, 1-505, 1-506, 1-507, 1-508, 1-509, 1-510, 1-511, 1-512, 1-513, 1-514, 1-515, 1-516, 1-517, 1-518, 1-519, 1-520, 1-521, 1-522, 1-523, 1-524, 1-525, 1-526, 1-527, 1-528, 1-529, 1-530, 1-531, 1-532, 1-533, 1-534, 1-535, 1-536, 1-537, 1-538, 1-539, 1-2564 and 1-2565.

[0066] The following compounds are even more preferred, that is Compounds No.: 1-457, 1-458, 1-459, 1-460, 1-461, 1-462, 1-463, 1-464, 1-465, 1-466, 1-467, 1-468, 1-469, 1-470, 1-471, 1-472, 1-473, 1-474, 1-475, 1-476, 1-477, 1-478, 1-479, 1-480, 1-481, 1-482, 1-483, 1-484, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-495, 1-496, 1-497, 1-498, 1-499, 1-500, 1-501, 1-502, 1-503, 1-504, 1-505, 1-506, 1-507, 1-508, 1-509, 1-510, 1-511, 1-512, 1-513, 1-514, 1-515, 1-516, 1-517, 1-518, 1-519, 1-520, 1-521, 1-522, 1-523, 1-524, 1-525, 1-526, 1-527, 1-528, 1-529, 1-530, 1-531, 1-532, 1-533, 1-534, 1-535, 1-536, 1-537, 1-538 and 1-539.

[0067] The following compounds are further preferred, that is Compounds No.: 1-496 and 1-539.

[0068] The most preferred compound is N-[5-(1,2-Dithiolan-3-yl)pentanoyl]methanesulphonamide (Compound No. 1-496); and pharmaceutically acceptable salts thereof.

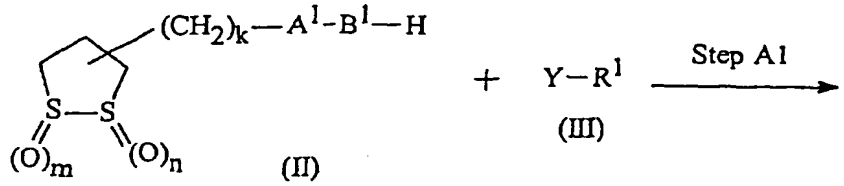
[0069] The compounds of the present invention may be prepared by a variety of methods well known for the preparation of compounds of this general type. For example, they may be prepared by the following Methods A to G.

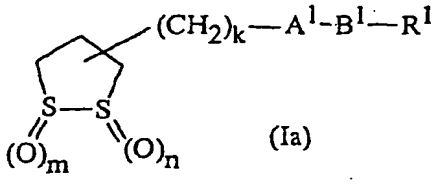
Method A

[0070] In this Method, a compound of formula (II) is reacted with a compound of formula (III), to give a compound of formula (Ia), which is a compound of formula (I) in which the meanings of A and B are somewhat restricted.

Reaction Scheme A:

[0071]





[0072] In the above formulae:

R^1, k, m and n are as defined above;

A^1 represents any of the groups defined above for A, other than the groups of formulae -CO-O- and -N(R^2)O- [in which R^2 is as defined above];

B^1 represents a group of formula -N(R^5)- or -N(R^5)N(R^6)- [in which R^5 and R^6 are as defined above]; and

Y represents a group to be eliminated.

[0073] There is no particular restriction on the group to be eliminated, provided that it can be eliminated as a nucleophilic residue, and examples of such groups are well known to those skilled in the art. Specific examples of such groups include:

halogen atoms, such as the chlorine, bromine and iodine atoms

trihalomethyl groups, such as the trichloromethyl group;

lower alkanesulphonyloxy groups, such as the methanesulphonyloxy and ethanesulphonyloxy groups;

lower haloalkanesulphonyloxy groups, such as the trifluoromethanesulphonyloxy and pentafluoroethanesulphonyloxy groups; and

arylsulphonyloxy groups, such as the benzenesulphonyloxy, p-toluenesulphonyloxy and p-nitrobenzenesulphonyloxy groups.

[0074] Of these, a halogen atom or an alkanesulphonyl group is preferred.

Step A1

[0075] In this Step, a dithiolan derivative of formula (Ia) is prepared by reacting a compound of formula (II) with a compound of formula (III) in a solvent in the presence of a base.

[0076] The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone and cyclohexanone; nitriles, such as acetonitrile, propionitrile and isobutyronitrile; amides, such as formamide, dimethylformamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide; sulphoxides, such as dimethyl sulphoxide; and sulphones, such as sulpholane. Of these, we prefer the ketones, ethers and amides, more preferably acetone, tetrahydrofuran, dimethylformamide and N,N-dimethylacetamide.

[0077] There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: inorganic bases, such as alkali metal carbonates (for example sodium carbonate, potassium carbonate, lithium carbonate or cesium carbonate), alkali metal hydrogencarbonates (for example sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate), alkali metal hydrides (for example lithium hydride, sodium hydride or potassium hydride), alkali metal or alkaline earth metal hydroxides (for example sodium hydroxide, potassium hydroxide, barium hydroxide or lithium hydroxide) and alkali metal fluorides (for example sodium fluoride or potassium fluoride); and alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide. Of these, the alkali metal carbonates, alkali metal hydrides and alkali metal alkoxides are preferred, and potassium carbonate, sodium hydride and potassium t-butoxide are most preferred.

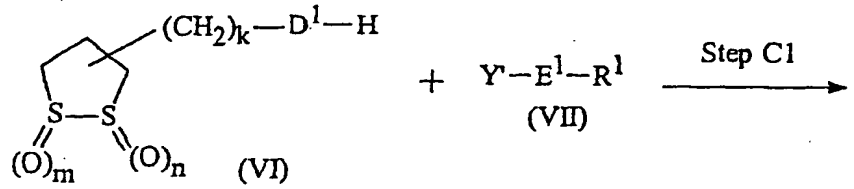
[0078] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 100°C, more preferably from 0°C to 50°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 24 hours, more preferably from 30 minutes to 12 hours, will usually suffice.

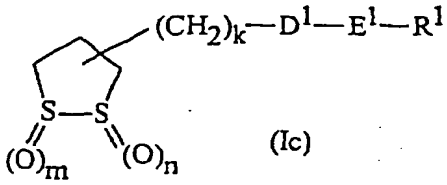
Method C

[0079] This demonstrates the preparation of a compound of formula (Ic), that is a compound of formula (I) in which A represents a group of formula $-CON(R^2)SO_2-$, and B represents a single bond.

Reaction Scheme C:

[0080]





[0081] In the above formulae:

R^1, k, m and n are as defined above,

D^1 represents an oxygen atom, or a group of formula $-N(R^2)-$, $-CON(R^2)-$, $-ON(R^2)-$, $-O-CON(R^2)-$, $-N(R^2)N(R^3)-$ or $-N(R^2)CON(R^3)-$[in which R^2 and R^3 are as defined above],

E^1 represents a carbonyl group, a sulphonyl group or a group of formula -COCO-, and

Y' represents a group to be eliminated, as in the definition of Y; however, the imidazolyl group, or an active ester residue, including acyloxy groups, such as the acetoxy group, or alkoxyacyloxy groups, such as the methoxyacetoxy group, are preferred.

Step C1

[0082] In this Step, a dithiolan derivative of formula (Ic) is prepared by acylating or sulphonylating a compound of formula (VI) with a compound of formula (VII) in a solvent in the presence of a base.

[0083] The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone and cyclohexanone; nitriles, such as acetonitrile, propionitrile and isobutyronitrile; and amides, such as formamide, dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide. Of these, the aromatic hydrocarbons, halogenated hydrocarbons, ethers and amides are preferred, and halogenated hydrocarbons, ethers and amides are more preferred.

[0084] There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: organic bases, such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, N-methyldicyclohexylamine, N-meth-

ylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo-[2.2.2] octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), of these, triethylamine and diisopropylethylamine are preferred.

[0085] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 100°C, more preferably from 0°C to 80°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 2 days, more preferably from 20 minutes to 1 day, will usually suffice.

[0086] As an alternative, where the compound of formula (VI) is reacted with a compound of formula (VII) in which E^1 represents a carbonyl group, the reaction may also be accomplished using a compound of formula HOOC-R^1 (in which R^1 is as defined above) by reacting the compound of formula (VI) with the compound of formula (VII) using a condensing agent in a solvent in the presence or absence of a base.

[0087] There is no particular restriction on the nature of the condensing agents used, and any condensing agent commonly used in reactions of this type may equally be used here. Examples of such condensing agents include:

(1) a combination of a phosphoric acid ester, such as diethyl cyanophosphate or diphenylphosphoryl azide, and the base described below;

(2) a carbodiimide, such as 1,3-dicyclohexylcarbodiimide, 1,3-diisopropylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; a combination of one or more of the above carbodiimides and the base described below; a combination of one or more of the above carbodiimides and an N-hydroxy compound, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole or N-hydroxy-5-norbomene-2,3-dicarboxyimide;

(3) a combination of a disulphide, such as 2,2'-dipyridyl disulphide or 2,2'-dibenzothiazolyl disulphide, and a phosphine, such as triphenylphosphine or tributylphosphine;

(4) a carbonate, such as N,N'-disuccinimidyl carbonate, di-2-pyridyl carbonate or S,S'-bis(1-phenyl-1H-tetrazol-5-yl)dithiocarbonate;

(5) a phosphinic chloride, such as N,N'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride;

(6) an oxalate, such as N,N'-disuccinimidyl oxalate, N,N'-diphthalimide oxalate, N,N'-bis(5-norbomene-2,3-dicarboxyimidyl) oxalate, 1,1'-bis(benzotriazolyl) oxalate, 1,1'-bis(6-chlorobenzotriazolyl) oxalate or 1,1'-bis(6-trifluoromethylbenzotriazolyl) oxalate;

(7) a combination of one or more of the above phosphines and an azodicarboxylic acid ester, such as diethyl azodicarboxylate, or an azodicarboxylic amide, such as 1,1'-(azodicarbonyl)dipiperidine; a combination of one or more of the above phosphines and the base described below;

(8) an N-lower alkyl-5-arylisoxazolium-3'-sulphonate, such as N-ethyl-5-phenylisoxazolium-3'-sulphonate;

(9) a diheteroaryldiselenide, such as di-2-pyridyl diselenide;

(10) an arylsulphonyltriazolide, such as p-nitrobenzenesulphonyltriazolide;

(11) a 2-halo-1-lower alkylpyridinium halide, such as 2-chloro-1-methylpyridinium iodide;

(12) an imidazole, such as 1,1'-oxalyldiimidazole or N,N'-carbonyldiimidazole;

(13) a 3-lower alkyl-2-halobenzothiazolium fluoroborate such as 3-ethyl-2-chloro-benzothiazolium fluoroborate;

(14) a 3-lower alkyl-benzothiazole-2-serone, such as 3-methyl-benzothiazol-2-serone;

(15) a phosphate, such as phenyldichlorophosphate or polyphosphate ester;

(16) a halosulphonyl isocyanate, such as chlorosulphonyl isocyanate;

(17) a halosilane, such as trimethylsilyl chloride or triethylsilyl chloride;

(18) a combination of a lower alkanesulphonyl halide, such as methanesulphonyl chloride and the base described below;

(19) an N,N,N',N'-tetra lower alkylhaloformamidium chloride, such as N,N,N',N'-tetramethylchloroformamidium chloride; and

(20) a combination of a lower alkyloxycarbonyl halide, such as ethyl chlorocarbonate and the base described below;

preferably the above (1), (2), (7), (12) and (20).

[0088] The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; nitriles, such as acetonitrile and isobutyronitrile; and amides, such as formamide, dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide.

[0089] There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: organic bases, such as N-methylmorpholine, triethylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline and N,N-diethylaniline.

[0090] If desired, 4-(N,N-dimethylamino)pyridine and 4-pyrrolidinopyridine can be combined with other bases and used in a catalytic amount. Also, in order to carry out the reaction more effectively, a dehydrating agent such as a molecular sieve, a quaternary ammonium salt (for example benzyltriethylammonium chloride or tetrabutylammonium chloride), a crown ether, such as dibenzo-18-crown-6, or an acid trapping agent, such as 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one, can be added to the reaction mixture.

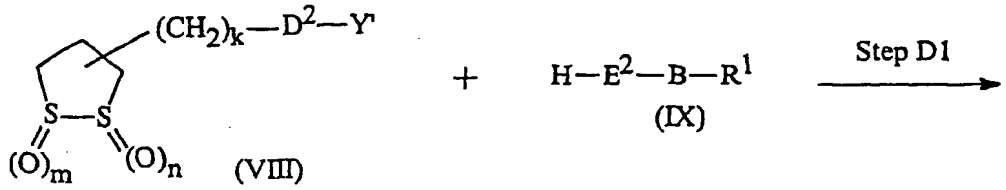
[0091] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 80°C, more preferably from 0°C to room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 3 days, more preferably from 30 minutes to 1 day, will usually suffice.

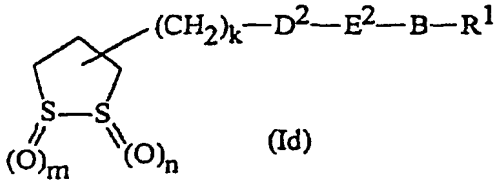
Method D

[0092] This demonstrates the preparation of a compound of formula (Id), that is a compound of formula (I) in which A represents a carbonyl group, or a group of formula $-CON(R^2)N(R^3)CO-$, $-CON(R^2)CO-$, $-CON(R^2)SO_2-$, $-CO-O-$, $-CO-CON(R^2)N(R^3)CO-$, $-CO-CON(R^2)CO-$ or $-CO-CON(R^2)SO_2-$ [in which R^2 and R^3 are as defined above].

Reaction Scheme D:

[0093]





[0094] In the above formulae:

B, R^1, Y', k, m and n are as defined above,

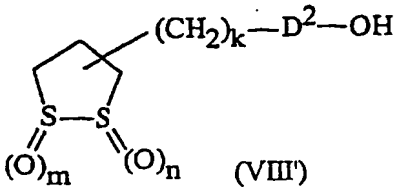
D^2 represents a carbonyl group, and

E^2 represents a group of formula $-N(R^2)SO_2-$ [in which R^2 is as defined above].

Step D1

[0095] In this Step, a dithiolan derivative of formula (Id) is prepared by acylating a compound of formula (IX) with a compound of formula (VIII) in a solvent in the presence of a base. The reaction is essentially the same as that described above in Step C1, and may be carried out using the same solvents, bases and reaction conditions.

[0096] Alternatively, the dithiolan derivative of formula (Id) can be prepared by reacting a compound of formula (VIII') with the compound of formula (IX) using a condensing agent in a solvent in the presence or absence of a base.



(in which D^2, k, m and n are as defined above.)

[0097] The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and

dichlorobenzene; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; nitriles, such as acetonitrile and isobutyronitrile; and amides, such as formamide, dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide.

[0098] There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: organic bases, such as N-methylmorpholine, triethylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline and N,N-diethylaniline.

[0099] If desired, 4-(N,N-dimethylamino)pyridine and 4-pyrrolidinopyridine can be combined with other bases and used in a catalytic amount. Also, in order to carry out the reaction more effectively, a dehydrating agent, such as a molecular sieve, a quaternary ammonium salt (for example benzyltriethylammonium chloride or tetrabutylammonium chloride), a crown ether, such as dibenzo-18-crown-6, or an acid trapping agent, such as 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one, can be added to the reaction mixture.

[0100] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 80°C, more preferably from 0°C to room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 3 days, more preferably from 30 minutes to 1 day, will usually suffice.

Method G

[0101] This illustrates the preparation of a compound of formula (I) in which at least one of m and n is 1 or 2, that is a compound of formula (Ig) from a compound of formula in which m and n are both zero, that is a compound of formula (Ig').

Reaction Scheme G:

[0102]

[0103] In the above formulae:

A, B, R^1 and k are as defined above; and

m' and n' are as defined above for m and n provided that at least one is not 0.

Step G1

[0104] In this Step, a dithiolan derivative of formula (Ig) is prepared by oxidizing a compound of formula (Ig') [a compound of formula (I) in which n and m are 0].

[0105] There is no particular restriction on the nature of the oxidizing agents used, and any oxidizing agent commonly used in reactions of this type may equally be used here, provided that it is capable of oxidising a sulphide to a sulphoxide or a sulphone. Examples of such oxidizing agents include: hydroperoxides, such as hydrogen peroxide, t-butyl hydroperoxide or pentyl hydroperoxide; dialkyl peroxides, such as di-t-butyl peroxide; peracids, such as perbenzoic acid,

m-chloroperbenzoic acid or peracetic acid; peracid esters, such as methyl perbenzoate; and diacyl peroxides, such as benzoyl peroxide. Of these, we particularly prefer hydrogen peroxide, m-chloroperbenzoic acid and t-butyl hydroperoxide.

[0106] The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone and cyclohexanone; nitriles, such as acetonitrile, propionitrile and isobutyronitrile; amides, such as formamide, dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulpholane; alcohols, such as methanol and ethanol; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; and water. Of these, we prefer the aromatic hydrocarbons, halogenated hydrocarbons, ketones, amides, alcohols and water, more preferably the halogenated hydrocarbons, ketones, amides, alcohols and water.

[0107] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -50 to 100°C, more preferably from -20 to 50°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 2 days, more preferably from 30 minutes to 12 hours, will usually suffice.

[0108] After completion of each of the above reactions, the desired compound may be recovered from the reaction mixture by conventional methods.

[0109] For example, the desired compound may be obtained by: suitably neutralising the reaction mixture; removing insolubles by filtration if insolubles exist; adding a water-immiscible organic solvent, such as ethyl acetate to the reaction mixture; washing with water or another suitable solvent; separating the organic layer containing the desired compound; drying it over a drying agent, such as anhydrous sodium sulphate or anhydrous magnesium sulphate; and removing the solvent, e.g. by evaporation.

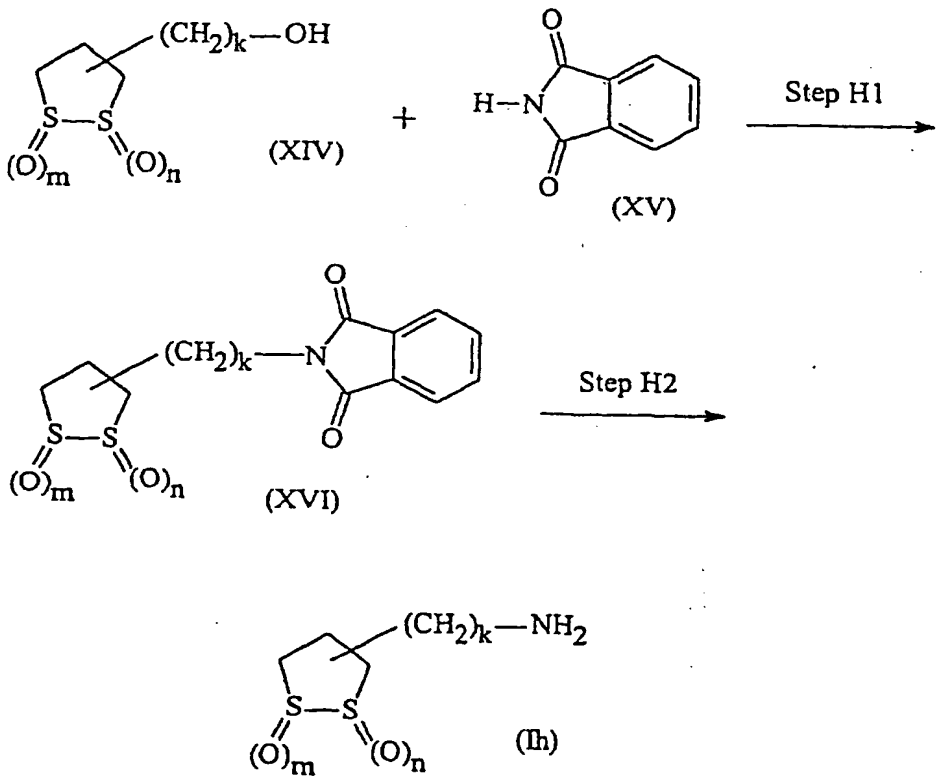
[0110] The compound thus obtained can be separated and purified, if necessary, by appropriately combining conventional methods, for example, recrystallization, reprecipitation or other methods commonly used in the separation and purification of organic compounds, for example, adsorption column chromatography using a carrier such as silica gel, alumina or magnesium-silica gel type Florisil; a method using a synthesized adsorbent such as partition column chromatography using a carrier such as Sephadex LH-20 (trade mark, manufactured by Pharmacia Co, Ltd.), Amberlite XAD-11 (trade mark, manufactured by Rohm and Haas Co. Ltd.) and Diaion HP-20 (trade mark, manufactured by Mitsubishi Kasei Corporation), a method using an ion exchange chromatogram, or normal phase-or reverse phase column chromatography using silica gel or alkylated silica gel (preferably high performance liquid chromatography), and eluting with a suitable eluent.

[0111] The starting materials in Methods A to G are known compounds or are compounds synthesized from known compound by conventional methods. For example, the amino derivative of formula (Ih), which is a starting material in Method A and Method C can be prepared by the following Method H.

Method H

Reaction Scheme H:

[0112]



[0113] In the above formulae: k, m and n are as defined above.

Step H1

[0114] In this Step, a phthalimide derivative of formula (XVI) is prepared by carrying out a Mitsunobu reaction between a compound of formula (XIV) and phthalimide of formula (XV).

[0115] There is no particular restriction on the nature of the reagents used in the Mitsunobu reaction, and any reagent commonly used in reactions of this type may equally be used here. Examples of such reagents include: a combination of an azo compound, such as a di-lower alkyl azodicarboxylate (for example dimethyl azodicarboxylate, diethyl azodicarboxylate or diisopropyl azodicarboxylate) or an azodicarboxamide [such as 1,1'-(azodicarbonyl)dipiperidine] and a phosphine, such as a triarylphosphine (for example triphenylphosphine) or a tri-lower alkyl phosphine (for example tributylphosphine), more particularly a combination of a di-lower alkyl azodicarboxylate and a triarylphosphine, most preferably a combination of dimethyl azodicarboxylate and triphenylphosphine.

[0116] The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether, diisopropyl ether, tetrahy-

drofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; nitriles, such as acetonitrile and isobutyronitrile; amides, such as formamide, dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide; and sulphoxides, such as dimethyl sulphoxide and sulpholane. Of these, we prefer the aromatic hydrocarbons and ethers.

[0117] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20 to 100°C, more preferably from 0 to 50°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 3 days, more preferably from 30 minutes to 12 hours, will usually suffice.

Step H2

[0118] In this Step, an amino derivative of formula (Ih) is prepared by reacting the phthalimide derivative of formula (XVI) with butylamine or hydrazine in a solvent. For example it may be accomplished by reacting the phthalimide derivative of formula (XVI) with butylamine in methanol at room temperature for 6 hours.

[0119] Since the dithiolan derivatives have the effect of increasing the activity of glutathione reductase, a composition which increases the activity of glutathione reductase, containing those compounds or pharmaceutically acceptable salts thereof can be used for the prevention or treatment of diseases resulting from oxidative stress. Examples of diseases resulting from oxidative stress are disease or pathologic states including damage caused by alcohol abuse, exposure to xenobiotic agents or radiation; intracellular oxidative states caused by hepatic diseases; intoxication from drugs and chemical agents (e.g. carcinostats including platinum chelate, antibiotics, antiparasitics, paraquat, carbon tetrachloride and halothane); intoxication from heavy metals; disorders of the nervous system including brain and neurone degenerative disorders (e.g. cerebral ischaemia, cerebral ictus, hypoglycaemia, epileptic attacks, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's chorea); diseases related to an altered functionality of the immune system, in particular tumour immunotherapy; infertility, in particular male infertility; coronary heart disease; ophthalmologic disorders such as cataract, retinopathy of prematurity and siderosis; pulmonary diseases such as idiopathic pulmonary fibrosis, adult respiratory distress syndrome, emphysema, asthma, bronchopulmonary dysplasia and interstitial pulmonary fibrosis; chronic renal failure; gastric ulcer; canceration and metastases of cancer including colorectal cancer; diabetes; hepatocyte necrosis and apoptosis including ethanol-induced hepatopathy; viral diseases including influenza, hepatitis B and HIV; abnormalities of blood or blood vessels such as Fanconi's anemia, septicemia, enhanced permeability through blood vessels and leukocyte adherence; various malformations such as Down's syndrome, Duchenne muscular dystrophy, Becker dystrophy, Dubin-Johnson-Spring syndrome and favism; and inflammatory diseases such as nephritis, pancreatitis, dermatitis, fatigue and rheumatism. In particular, the dithiolan derivatives and pharmaceutically acceptable salts thereof of the present invention are useful for the prevention or treatment of diseases or pathologic states such as damage caused by radiation, intracellular oxidative states caused by hepatic diseases, intoxication (i.e. side effects) from carcinostats including platinum chelate, disorders of the nervous system, cataract, diabetes, hepatocyte necrosis and apoptosis, viral diseases, and inflammatory diseases.

[0120] Among the above-described diseases resulting from oxidative stress, there are some diseases where the effects are irreversible, once they have occurred. A therapeutic agent for such a disease means a medicament which prevents or delays the progress of the disease.

[0121] The dithiolan derivatives of formula (I) or pharmaceutically acceptable salts thereof of the present invention can be used together with a medicament which is known as a preventive agent or therapeutic agent for a disease listed above as the diseases resulting from oxidative stress and may show a synergistic effect.

[0122] Cyanamide, disulphiram, adenine and cysteine are known as medicaments for treating the damage caused by alcohol abuse, exposure to xenobiotic agents or radiation; aminoethylsulphonic acid, protoporphyrin disodium and diisopropylamine dichloroacetate are known as medicaments for treating intracellular oxidative states caused by hepatic diseases; glutathione, dimercaprol, and calcium disodium edetate are known as medicaments for treating intoxication from drugs and chemical agents (e.g. carcinostats including platinum chelate, antibiotics, antiparasitics, paraquat, carbon tetrachloride and halothane) or for treating intoxication from heavy metals; phenobarbital, phenytoin, bromocriptine mesylate, sulpiride, sodium valproate, haloperidol, levodopa-carbidopa, idebenone and aniracetam are known as medicaments for treating disorders of the nervous system including brain and neurone degenerative disorders (e.g. cerebral ischaemia, cerebral ictus, hypoglycaemia, epileptic attacks, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's chorea); cyclophosphamide, interferon-α and interferon-β are known as medicaments for treating diseases related to an altered functionality of the immune system, in particular tumour immunotherapy; sildenafil is known as a medicament for treating infertility, in particular male infertility; digitoxin and digoxin are known as medicaments for treating coronary heart disease; pirenoxine is known as a medicament for

treating ophthalmologic disorders such as cataract, retinopathy of prematurity and siderosis; theophylline, ketotifen fumarate, epinastine hydrochloride, pranlukast and suplatast tosylate are known as medicaments for treating pulmonary diseases such as idiopathic pulmonary fibrosis, adult respiratory distress syndrome, emphysema, asthma, bronchopulmonary dysplasia and interstitial pulmonary fibrosis; furosemide, etacrynic acid and bumetanide are known as medicaments for treating chronic renal failure; teprenone, rebamipide, ecabet sodium, plaunotol, famotidine, ranitidine hydrochloride and lansoprazole are known as medicaments for treating gastric ulcer; BB-2516 and AG3340 are known to be useful against canceration and metastases of cancer including colorectal cancer; epalrestat, voglibose, acarbose, insulin, glibenclamide and troglitazone are known as medicaments for treating diabetes; aminoethylsulphonic acid, protoporphyrin disodium and diisopropylamine dichloroacetate are known as medicaments for treating hepatocyte necrosis and apoptosis including ethanol-induced hepatopathy; acyclovir, zidovudine, interferon-α, interferon-β and interferon-γ are known as medicaments for treating viral diseases including influenza, hepatitis B and HIV; erythropoietin derivatives are known as medicaments for treating abnormalities of the blood or blood vessels such as Fanconi's anemia, septicemia, enhanced permeability through blood vessels and leukocyte adherence; fenipentol, camostat mesylate, indomethacin, loxoprofen sodium and diclofenac sodium are known as medicamenst for treating inflammatory diseases such as nephritis, pancreatitis, dermatitis, fatigue and rheumatism.

[0123] The compounds of the present invention can be administered in any conventional pharmaceutical formulation, the nature of which will depend on the patient and the intended route of administration. For example for oral administration, suitable formulations include tablets, capsules, granules, powders or syrups. For parenteral administration suitable formulations include injections or suppositories. These formulations can be prepared by well-known methods using additives such as excipients, lubricants, binders, disintegrating agents, stabilizers, corrigents and diluents.

[0124] Examples of suitable excipients include organic excipients, for example: sugar derivatives such as lactose, sucrose, glucose, mannitol or sorbitol; starch derivatives such as corn starch, potato starch, α-starch, dextrin or carboxymethyl starch; cellulose derivatives such as crystalline cellulose, low substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium or internally bridged carboxymethylcellulose sodium; gum arabic; dextran; and Pullulan; inorganic excipients including silicate derivatives such as light silicic acid anhydride, synthetic aluminium silicate or magnesium meta-silicic acid aluminate; phosphates such as calcium phosphate; carbonates such as calcium carbonate; and sulphates such as calcium sulphate.

[0125] Examples of suitable lubricants include stearic acid, metal stearates such as calcium stearate or magnesium stearate; talc; colloidal silica; waxes such as beeswax or spermaceti; boric acid; adipic acid; sulphates such as sodium sulphate; glycol; fumaric acid; sodium benzoate; DL-leucine; sodium salts of fatty acids; lauryl sulphates such as sodium lauryl sulphate or magnesium lauryl sulphate; silicates such as silicic acid anhydride or silicic acid hydrate; and the foregoing starch derivatives.

[0126] Examples of suitable binders include polyvinylpyrrolidone, Macrogol, and similar compounds to the excipients described above.

[0127] Examples of suitable disintegrating agents include similar compounds to the excipients described above; and chemically modified starches or celluloses such as crosscarmelose sodium, sodium carboxymethylstarch or bridged polyvinylpyrrolidone.

[0128] Examples of suitable stabilisers include paraoxybenzoates such as methylparaben or propylparaben; alcohols such as chlorobutanol, benzyl alcohol or phenylethyl alcohol; benzalkonium chloride; phenols such as phenol or cresol; thimerosal; dehydroacetic acid; and sorbic acid.

[0129] Examples of suitable corrigents include sweeteners, vinegar or perfumes such as those conventionally used.

[0130] Moreover, since the dithiolan derivative or the pharmaceutically acceptable salt thereof of the present invention is less stimulating for the eyes, it can be topically administered to the eyes. Suitable formulations for the topical administration to the eyes include solutions, suspensions, gels, ointments and solid inserting agents.

[0131] The formulation of these compositions for topical administration may contain the dithiolan derivative or the pharmaceutically acceptable salt thereof at a level of from 0.001% (preferably 0.01%) as a lower limit to 10% (preferably 5%) as an upper limit.

[0132] The pharmaceutical formulation containing an active compound can, if desired, be mixed with a non-toxic inorganic or organic carrier for pharmaceuticals.

[0133] Typical pharmaceutically acceptable carriers include water, a mixture of water and a water-miscible solvent such as a lower alkanol or aralkanol, a vegetable oil, polyalkylene glycol, a jelly using a petroleum as a base material, ethylcellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other acceptable carriers which can be preferably used. The formulation may contain non-toxic auxiliary substances such as an emulsifier, a preservative, a wetting agent and an excipient, for example, polyethylene glycol 200, 300, 400 and 600, carbowax 1000, 1500, 4000, 6000 and 10000, p-hydroxybenzoic acid esters such as methyl p-hydroxybenzoate or propyl p-hydroxybenzoate, a quaternary ammonium compound (for example, benzetonium chloride or benzalkonium chloride) which are known as compounds having anti-fungal properties at low temperatures and are non-toxic when used, an anti-fungal agent such as a phenyl mercury salt, a buffering component such as thimerosal, methyl- and propylparaben,

benzyl alcohol, phenylethanol, sodium chloride, sodium borate and sodium acetate, a gluconic acid buffering agent and sorbitan monolaurate, triethanolamine, polyoxyethylenesorbitan monopalmitate, sodium dioctyl sulphosuccinate, monothioglycerol, thiosorbitol and ethylenediaminetetraacetic acid.

[0134] Ophthalmological excipients can be used as a desired support medium for the compounds of the present invention and examples include the usual phosphoric acid buffering excipients (for example, a sodium phosphate buffer or a potassium phosphate buffer), isotonic boric acid excipients, isotonic sodium chloride excipients and isotonic sodium borate excipients.

[0135] As a further alternative, the pharmaceutical formulation may have the form of a solid insert which remains almost intact after the formulation has been administered, or it may also be formulated as a disintegrating insert which dissolves in the tear fluid or is disintegrated by other methods.

[0136] The dose of the dithiolan derivative of formula (I) or the pharmaceutically acceptable salt thereof of the present invention will vary, depending upon the condition and age of the patient and the form and route of administration. However, for example, in the case of oral administration, for an adult human patient, it is desirable to administer from 0.1 mg (preferably 1 mg) as a lower limit to 10000 mg (preferably 5000 mg) as an upper limit per day. In the case of intravenous administration, it is desirable to administer from 0.01 mg (preferably 0.1 mg) as a lower limit to 5000 mg (preferably 2000 mg) as an upper limit per day. In the case of topical administration to the eyes, it is desirable to administer from 0.001 mg (preferably 0.01 mg) as a lower limit to 500 mg (preferably 200 mg) as an upper limit per day. All of the above may be administered as a single dose or in divided doses. The dose and dosage regime will depend on the condition of the patient.

[0137] Pharmaceutical preparations of the present invention are illustrated by the following non-limiting Formulation Examples.

FORMULATION EXAMPLE 1

Powder

[0138] 5 g of N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (the compound of Example 2 hereafter), 895 g of lactose and 100 g of corn starch are mixed by means of a blender to obtain a powder.

FORMULATION EXAMPLE 2

Granules

[0139] 5 g of N-[5-(1,2-dithiolan-3-yl)pentanoyl]sulphamide (the compound of Example 7 hereafter), 865 g of lactose and 100 g of low substituted hydroxypropylcellulose are mixed. 300 g of a 10% w/v aqueous solution of hydroxypropyl cellulose are then added to the mixture, and then the resulting mixture is kneaded. The mixture is then granulated using an extruding granulator, after which it is dried to obtain a granule formulation.

FORMULATION EXAMPLE 4

Tablet

[0140] 5 g of (R)-N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (the compound of Example 40 hereafter), 90 g of lactose, 34 g of corn starch, 20 g of crystalline cellulose and 1 g of magnesium stearate are mixed by means of a blender. The mixture is then pelletised by means of a tablet making machine to obtain tablets.

FORMULATION EXAMPLE 5

Eye drops

[0141] The following components are mixed:

(R)-N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (the Compound of Example 40)	0.2 g
Disodium phosphate	0.716 g
Sodium phosphate	0.728 g
Sodium chloride	0.400 g
Methyl p-hydroxybenzoate	0.026 g

(continued)

Propyl p-hydroxybenzoate	0.014 g
Sterilised purified water	q.s.
Sodium hydroxide	q.s.
Total	100 ml

[0142] The pH of the mixture is adjusted to 7.0 and eye drops are prepared by a conventional method.

FORMULATION EXAMPLE 6

Eye drops

[0143] The following components are mixed:

(R)-N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (the Compound of Example 40)	0.2 g
Disodium phosphate	0.716 g
Sodium phosphate	0.728 g
Sodium chloride	0.400 g
Methyl p-hydroxybenzoate	0.026 g
Propyl p-hydroxybenzoate	0.014 g
Sterilised purified water	q.s.
Ascorbic acid	q.s.
Sodium hydroxide	q.s.
Total	100 ml

[0144] The pH of the mixture is adjusted to 7.0 and eye drops are prepared by a conventional method.

BIOLOGICAL ACTIVITY

[0145] The biological activity of the compounds of the present invention is illustrated by the following Test Examples.

TEST EXAMPLE 1

Measurement of Glutathione Reductase Activity

(a) Lens Tissue Culture

[0146] The test animals were 6 to 8 week old male SD rats (supplier: Nippon SLC). The animals were sacrificed by suffocation by inhalation of carbon dioxide. Both eyeballs of each test animal were then excised. An incision was made in the sclera on the back of the eyeballs, and then the vitreous body and iris-ciliary body were removed, followed by removal of the lens.

[0147] Each lens obtained in this manner was cultured by immersing it in 3 ml of the culture solution described below in a 6-well tissue culture plate (FALCON). Culturing was performed for 72 hours in a CO_2 incubator maintained at 37°C and 100% humidity in the presence of 5% CO_2 (in air).

[0148] Medium 199 (Gibco) containing penicillin (20 units/ml) and streptomycin (20 µg/ml) was used as the control culture solution.

[0149] The test culture solution contained the test compound added to the above-mentioned culture solution. The cultured lenses were placed in frozen storage until the time of the test.

(b) Measurement of Glutathione Reductase Activity

[0150] After homogenising each frozen rat lens in 2 ml of distilled water, the resulting homogenate was separated by centrifugation (10,000 g, 20 minutes) after which the resulting supernatant was used as the enzyme sample.

[0151] 400 µl of enzyme sample were added to 0.6 ml of phosphate buffer containing 1 mM oxidized glutathione

(GSSG) and 100 μM NADPH. After the mixture had reacted at 25°C for 6 minutes, the absorbance of the reaction mixture (at 340 nm: i.e. OD_{340nm}) was measured. The difference (ΔOD_{340nm}) between the OD_{340nm} value before reaction and the OD_{340nm} value after completion of the reaction was used as an indicator of glutathione reductase activity.

[0152] The results for the compound of Example 2 are shown in the following Table 4.

Table 4

Concentration of the compound of Example 2 (μM)	ΔOD_{340nm}/min/g protein
0	3.10±0.11
10	3.24±0.10
30	3.20±0.09
100	3.59±0.05 ($p<0.05$)
300	3.70±0.08 ($p<0.05$)
1000	4.16±0.18 ($p<0.05$)

[0153] The dithiolan derivatives of the present invention exhibited excellent glutathione reductase activity enhancing effects.

TEXT EXAMPLE 2

Anti-cataract Test

[0154] The test animals were 6 week old male SD rats (supplier: Nippon SLC). The animals were sacrificed by suffocation by inhalation of carbon dioxide. Both eyeballs of each test animal were then excised. The excised lenses were cultured at 37°C for 24 hours in Medium 199 (Gibco) containing 0.05 mg/ml of the test compound and 5 mM hydrogen peroxide. For the control test, excised lenses were cultured at 37°C for 24 hours in normal culture liquid (Medium 199, Gibco) or Medium 199 (Gibco) containing 5 mM hydrogen peroxide.

[0155] After culturing for 24 hours, the lenses were washed with physiological saline. Surface moisture was removed by placing the lenses on a piece of filter paper, and then the lenses were placed on a slide glass after which lens turbidity was scored under stereomicroscope from "-" (turbidity degree of the lens cultured in a normal culture medium) to "++++" (turbidity degree of the lens cultured in a medium containing hydrogen peroxide). The results are shown in Table 5.

Table 5

Compound of Example No.	Rat Lens turbidity in 5 mM H_2O_2, 24 hours
2	++
7	+

Table 5 (cont.)

Compound of Example No.	Rat Lens turbidity in 5 mM H_2O_2, 24 hours
lipoic acid	+++
normal lens	-
without drug	++++

[0156] As can be seen from the above results, the compounds of the present invention substantially improve the opacity of the lens.

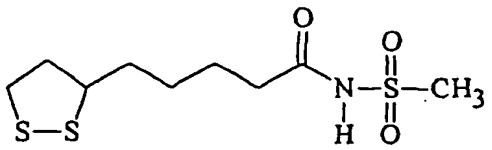
EXAMPLES

[0157] The present invention is further illustrated by reference to the following non-limiting Examples.

EXAMPLE 2

N-[5-(1,2-Dithiolan-3-yl)pentanoyl]methanesulphonamide (Compound No. 1-496)

[0158]



(a) 0.88 g of sodium hydride (as a 55% by weight dispersion in mineral oil) was washed with hexane, and 20 ml of dimethylformamide and 1.96 g of methanesulphonamide were added to the dispersion at room temperature. The resulting mixture was subjected to ultrasonic treatment for three hours and then left to stand at room temper-

ature overnight, to give reaction mixture (A).

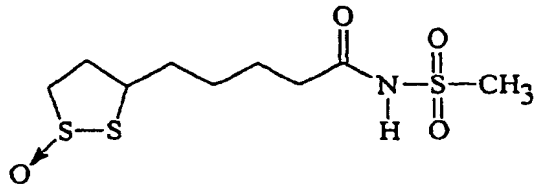
Separately, 2.06 g of D,L-α-lipoic acid were dissolved in 20 ml of dimethylformamide, and 1.63 g of N,N'-carbonyldiimidazole were added to the solution, whilst ice-cooling. The resulting mixture was then left to stand at room temperature overnight. At the end of this time, the reaction mixture was added dropwise to the above reaction mixture (A) at room temperature, and the mixture was stirred for 7 hours. The reaction mixture was then heated at 130°C for 3 hours, after which it was left to cool, and then poured into ice-water. Diluted aqueous hydrochloric acid was added to the mixture to adjust the pH to 5, and the mixture was extracted with ethyl acetate. The extraction solution was washed three times with a saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 4 : 1 by volume mixture of ethyl acetate and hexane and then ethyl acetate alone as the eluent, to obtain 0.12 g of the title compound, melting at 87°C to 88°C.

(b) 25.0 g of D,L-α-lipoic acid were dissolved in 500 ml of anhydrous dimethylformamide, and 21.57 g of N,N'-carbonyldiimidazole were added to the solution, whilst ice-cooling, after which the resulting mixture was stirred at room temperature for 2 hours and 30 minutes. 12.65 g of methanesulphonamide and 5.80 g of sodium hydride (as a 55% w/w dispersion in mineral oil) were then added, whilst ice-cooling, to the reaction mixture, and the mixture was stirred at room temperature for 4 hours and then left to stand at room temperature overnight. At the end of this time, the solvent was removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate, and then the solvent was removed by evaporation under reduced pressure. The residue thus obtained was purified by silica gel column chromatography, using 1:1, 2:1 and 3:1 by volume mixtures of ethyl acetate and hexane as eluent, to obtain 19.85 g of the title compound, melting at 85°C to 88°C.

EXAMPLE 3

N-[5-(1-Oxo-1,2-dithiolan -3-yl)pentanoyl]methanesulphonamide (Compound No. 2-496)

[0159]



[0160] 500 mg of N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (prepared as described in Example 2) were dissolved in 10 ml of acetone, and 0.44 ml of a 31% w/v aqueous solution of hydrogen peroxide was added to the solution, whilst ice-cooling. The mixture was stirred and then left to stand at room temperature overnight. At the end of this time, a further 0.2 ml of a 31% w/v aqueous solution of hydrogen peroxide was added to the reaction mixture, and then the mixture was stirred at room temperature for 30 minutes, and then stirred on an oil bath at 50°C for 1 hour. The mixture was then left to stand at room temperature for 3 days, after which it was stirred on an oil bath at 50°C for 10 hours; it was then left to stand at room temperature overnight. The solvent was then removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue thus obtained, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate, and then the solvent was removed by evaporation under reduced pressure. The residue thus obtained was purified by reverse phase preparative silica gel column chromatography, using 1 : 3 and 2 : 3 by volume mixtures of acetonitrile and water as the eluent. The solvent was evaporated from the eluted fraction thus obtained under reduced pressure, and the fraction was lyophilised, to obtain 0.15 g of the title compound (diastereomer mixture) as a colorless oil having an Rf value of 0.43 (silica gel thin layer chromatography, using a 10 : 1 by volume mixture of ethyl acetate and methanol as the developing solvent).

EXAMPLE 4

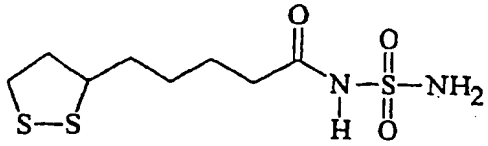
N-[5-(1,2-Dithiolan-3-yl)pentanoyl]methanesulphonamide sodium salt (Compound No. 1-496.sodium salt)

[0161] 750 mg of N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (prepared as described in Example 2) were dissolved in 15 ml of ethyl acetate, and 482 mg of sodium 2-ethylhexanoate was added to the mixture at room temperature. The mixture was stirred for 2 hours, after which it was left to stand for 2 days at room temperature. The crystals which precipitated from the reaction mixture were collected by filtration, to obtain 550 mg of the title compound, melting at 202°C to 204°C.

EXAMPLE 7

N-[5-(1,2-Dithiolan-3-yl)pentanoyl]sulphamide (Compound No. 1-539)

[0162]

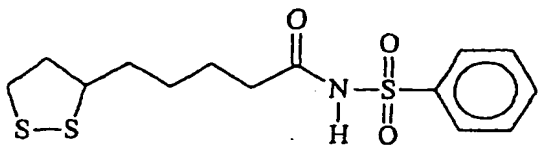


[0163] 50 mg of D,L-α-lipoic acid were dissolved in 10 ml of anhydrous dimethylformamide, and 421 mg of N,N'-carbonyldiimidazole were added to the solution, whilst ice-cooling, and then the mixture was stirred at room temperature for 3 hours. 461 mg of sulphamide and 113 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were then added to the reaction mixture, whilst ice-cooling, and the mixture was stirred for 4 hours and then left to stand at room temperature overnight. At the end of this time, the solvent was removed from the reaction mixture by evaporation under reduced pressure, and water and 2 N aqueous hydrochloric acid were added to the residue thus obtained to adjust the pH to 5 to 6, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate, and then the solvent was removed by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 3 : 2 and then a 2 : 1 by volume mixture of ethyl acetate and hexane as the eluent, and the resulting fraction was then recrystallized from a 1 : 2 : 1 by volume mixture of ethanol, diisopropyl ether and hexane, to obtain 119 mg of the title compound, melting at 141 °C to 142°C.

EXAMPLE 10

N-[5-(1,2-Dithiolan-3-yl)pentanoyl]benzenesulphonamide (Compound No. 1-457)

[0164]



[0165] 1.00 g of D,L-α-lipoic acid was dissolved in 20 ml of anhydrous dimethylformamide, and 0.86 g of N,N'-carbonyldiimidazole was added to the solution, whilst ice-cooling. The mixture was then stirred at room temperature for 2 hours and 30 minutes. 0.83 g of benzenesulphonamide and 0.23 g of sodium hydride (as a 55% w/w dispersion in mineral oil) were added to the reaction mixture, whilst ice-cooling, and the mixture was stirred for 2 hours. The solvent was then removed from the reaction mixture by evaporation under reduced pressure, and water and 2 N aqueous hydrochloric acid were added to the residue thus obtained to adjust the pH to 2, after which it was extracted with ethyl

acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate, and then the solvent was removed by evaporation under reduced pressure. The residue thus obtained was purified by silica gel column chromatography, using 1 : 2, 1:1 1 and 2 : 1 by volume mixtures of ethyl acetate and hexane as eluent, and then by reverse phase preparative silica gel column chromatography, using 3 : 7, 1 : 1 and 7 : 3 by volume mixtures of acetonitrile and water as eluent. The solvent was evaporated under reduced pressure from the fraction containing the title compound, and the residue thus obtained was dissolved in dioxane. The resulting solution was lyophilised, to obtain 0.61 g of the title compound having an Rf value of 0.51 (silica gel thin layer chromatography; using a 2 : 1 by volume mixture of ethyl acetate and hexane as the developing solvent).

EXAMPLE 11

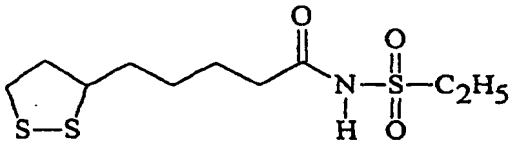
N-[5-(1,2-Dithiolan -3-yl)pentanoyl]benzenesulphonamide sodium salt (Compound No. 1-457.sodium salt)

[0166] 492 mg of N-[5-(1,2-dithiolan-3-yl)pentanoyl]benzenesulphonamide (prepared as described in Example 10) were dissolved in a mixture of 8 ml of ethyl acetate and 1 ml of tetrahydrofuran, and 283 mg of sodium 2-ethylhexanoate were added to the mixture at room temperature. The resulting mixture was stirred for 1 hour and 30 minutes, after which it was left to stand for 2 days. The crystals which precipitated from the reaction mixture were collected by filtration to obtain 349 mg of the title compound, melting at 213°C to 215°C.

EXAMPLE 20

N-[5-(1,2-Dithiolan-3-yl)pentanoyl]ethanesulphonamide (Compound No. 1-497)

[0167]

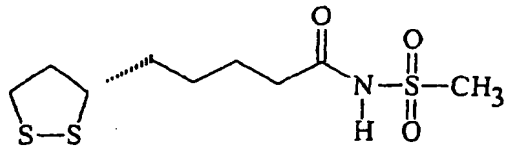


[0168] 500 mg of D,L-α-lipoic acid were dissolved in 10 ml of anhydrous dimethylformamide, and 428 mg of N,N'-carbonyldiimidazole were added to the solution, whilst ice-cooling. The mixture was then stirred at room temperature for 1 hour. At the end of this time, a solution of 284 mg of ethanesulphonamide in 3 ml of dimethylformamide and 113 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were added to the reaction mixture, whilst ice-cooling, and the mixture was stirred at room temperature for 1 hour and then left to stand for 3 days. The solvent was then removed from the reaction mixture by evaporation under reduced pressure, and water and 2 N aqueous hydrochloric acid were added to the residue thus obtained to adjust the pH to 2, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate, and then the solvent was removed by evaporation under reduced pressure. The residue thus obtained was purified by silica gel column chromatography, using 1 : 1 and 2 : 1 by volume mixtures of ethyl acetate and hexane as eluent, followed by reverse phase preparative silica gel column chromatography, using 3 : 7, 2 : 3 and 1 : I by volume mixtures of acetonitrile and water as eluent. The solvent was then removed from the eluted fraction thus obtained by evaporation under reduced pressure, and the residue thus obtained was dissolved in dioxane. The solution was lyophilised, to obtain 30 mg of the title compound, melting at 98°C to 100°C.

EXAMPLE 39

(S)-N-[5-(1,2-Dithiolan-3-yl)pentanoyl]methanesulphonamide (Compound No. 1-496)

[0169]

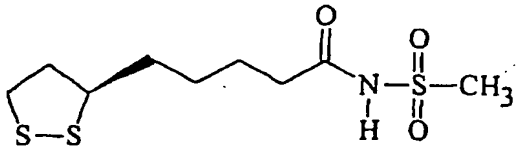


[0170] 300 mg of (S)-α-lipoic acid were dissolved in 6 ml of anhydrous dimethylformamide, and 276 mg of N,N'-carbonyldiimidazole and 1 ml of anhydrous dimethylformamide were added to the solution, whilst ice-cooling. The mixture was then stirred at room temperature for 1 hour and 30 minutes. At the end of this time, 162 mg of methanesulphonamide and 74 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were added to the reaction mixture, whilst ice-cooling, and the mixture was stirred at room temperature for 1 hour and then left to stand for 2 days. The solvent was then removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue thus obtained, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The solvent was then removed from the extraction solution by evaporation under reduced pressure. The residue thus obtained was purified by silica gel column chromatography, using 1 : 1 and 3 : 1 by volume mixtures of ethyl acetate and hexane as eluent. It was then recrystallized from a 1 : 2 by volume mixture of ethyl acetate and hexane, to obtain 154 mg of the title compound, melting at 91°C to 92°C.

EXAMPLE 40

(R)-N-[5-(1,2-Dithiolan -3-yl)pentanoyl]methanesulphonamide (Compound No. 1-496)

[0171]

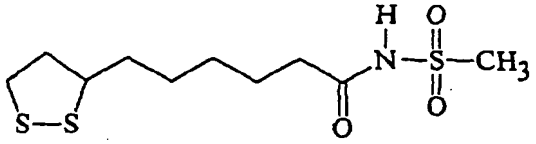


[0172] 100 mg of (R)-α-lipoic acid were dissolved in 2 ml of anhydrous dimethylformamide, and 97 mg of N,N'-carbonyldiimidazole were added to the solution, whilst ice-cooling. The mixture was then stirred at room temperature for 4 hours. At the end of this time, 57 mg of methanesulphonamide and 26 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were added to the reaction mixture, whilst ice-cooling, and the mixture was stirred at room temperature for 5 hours and then left to stand overnight. The solvent was then removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue thus obtained. The resulting mixture was neutralized by the addition of 2 N aqueous hydrochloric acid, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulphate. The solvent was removed from the extraction solution by evaporation under reduced pressure. The residue thus obtained was purified by silica gel column chromatography, using 1 : 1 and 3 : 1 by volume mixtures of ethyl acetate and hexane as eluent, after which it was dissolved in dioxane and lyophilised, to obtain 68 mg of the title compound, melting at 71°C to 73°C.

EXAMPLE 107

N-[6-(1,2-Dithiolan-3-yl)hexanoyl]methanesulphonamide (Compound No. 1-1796)

[0173]

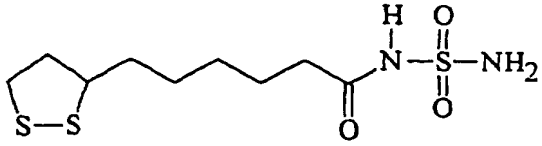


[0174] 6 ml of anhydrous dimethylformamide and 276 mg of N,N'-carbonyldiimidazole were added to 10 ml of a solution of 1.5 mmol of 6-(1,2-dithiolan-3-yl)hexanoic acid (prepared as described in Preparation 2) in toluene, and the mixture was stirred at room temperature for 4 hours and 30 minutes. 162 mg of methanesulphonamide and 74 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were then added to the reaction solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was then left to stand at room temperature overnight, and the solvent was removed from the reaction mixture by evaporation under reduced pressure. Water was added to the residue, and the mixture was washed with ethyl acetate and neutralized by the addition of 2 N aqueous hydrochloric acid, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the extraction solution by evaporation under reduced pressure, and the residue was subjected to silica gel column chromatography, using a 2 : 1 by volume mixture of ethyl acetate and hexane as the eluent). The solvent was evaporated from the eluate, and the residue was again subjected to silica gel column chromatography, using 2 : 3 and 3 : 2 by volume mixtures of ethyl acetate and hexane as the eluent. The solvent was removed from the eluate by evaporation under reduced pressure, and the residue was dissolved in dioxane and then lyophilised. to obtain 98 mg of the title compound as a yellow oil having an Rf value of 0.37 (silica gel thin layer chromatography; using a 3 : 2 by volume mixture of ethyl acetate and hexane as developing solvent).

EXAMPLE 112

N-[6-(1,2-Dithiolan-3-yl)hexanoyl] sulphamide (Compound No. 1-1839)

[0175]

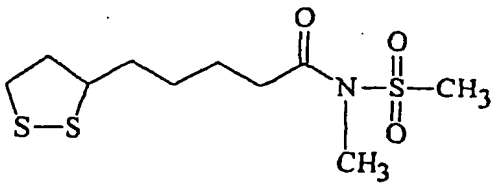


[0176] The reaction was carried out as described in Example 107, but using 5 ml of a solution of 1.6 mmol of 6-(1,2-dithiolan-3-yl)hexanoic acid (prepared as described in Preparation 2) in toluene, 7 ml of anhydrous dimethylformamide, 308 mg of N,N'-carbonyldiimidazole, 365 mg of sulphamide and 83 mg of sodium hydride (as a 55% w/w dispersion in mineral oil). The solvent was removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue, after which it was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the extraction solution by evaporation under reduced pressure, and the residue was subjected to silica gel column chromatography, using 3 : 2 and 2 : 1 by volume mixtures of ethyl acetate and hexane as the eluent. The solvent was removed from the eluate by evaporation under reduced pressure, and the residue was recrystallized from a 1 : 2 by volume mixture of ethyl acetate and hexane, to obtain 92 mg of the title compound as pale yellow crystals, melting at 130 to 132°C.

EXAMPLE 125

N-[5-(1,2-Dithiolan-3-yl)pentanoyl]-N-methylmethanesulphonamide (Compound No. 1-2672)

[0177]

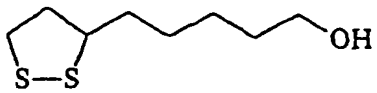


[0178] 40 mg of copper chloride were added to 20 ml of a solution of 1.36 g of dicyclohexylcarbodiimide in anhydrous methanol, and the mixture was left to stand at room temperature for one and one half hours. The solvent was then removed from the mixture by distillation under reduced pressure. 20 ml of anhydrous dimethylformamide and 1.00 g of N-[5-(1,2-dithiolan-3-yl)pentanoyl]methanesulphonamide (prepared as described in Example 2) were then added to the residue. and the mixture was stirred at 70°C on an oil bath for an hour. The mixture was then left to stand at room temperature overnight, after which it was stirred at 70°C on an oil bath for 1 hour, and the solvent was removed from the reaction mixture by evaporation under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. Insoluble material in the extract was removed by filtration, and the filtrate was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the solution by evaporation under reduced pressure, and the residue was subjected to silica gel column chromatography, using 2 : 3 and 1 : 1 by volume mixtures of ethyl acetate and hexane as the eluent. The solvent was removed from the eluate by evaporation under reduced pressure, and the residue was subjected to reverse phase preparative silica gel column chromatography, using 1 : 1 and 3 : 2 by volume mixtures of acetonitrile and water as eluent. The acetonitrile was then removed from the solution by evaporation under reduced pressure, after which the residue was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the extraction solution by evaporation under reduced pressure, and the residue was dissolved in dioxane and then lyophilised, to obtain 660 mg of the title compound as a pale yellow amorphous substance having an Rf value of 0.27 (silica gel thin layer chromatography, using a 2 : 3 by volume mixture of ethyl acetate and hexane as developing solvent).

PREPARATION 1

5-(1,2-Dithiolan-3-yl)pentanol

[0179]



[0180] 44 ml of a hexane solution containing 2.0 M of (trimethylsilyl)diazomethane was added dropwise, whilst ice-cooling, to a mixture of 15.00 g of D,L-α-lipoic acid in 15 ml of methanol and 150 ml of toluene, and then the mixture was stirred at room temperature for one hour. 11 ml of a hexane solution containing 2.0 M of (trimethylsilyl)diazomethane were then added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was then allowed to stand at room temperature for 2 days. The solvent was then removed by distillation under reduced pressure from the reaction mixture, to give ethyl 5-(1,2-dithiolan-3-yl)pentanoate as a yellow oil.

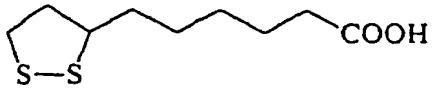
[0181] A solution of ethyl 5-(1,2-dithiolan-3-yl)pentanoate in 40 ml of anhydrous tetrahydrofuran was added dropwise, whilst cooling with ice and sodium chloride, to a suspension of 3.34 g of lithium aluminium hydride in 150 ml of anhydrous tetrahydrofuran. The resulting mixture was stirred at room temperature for 3 hours and 30 minutes. Sodium sulphate

decahydrate was then added, whilst cooling with ice and sodium chloride, to the reaction mixture, and then the mixture was stirred at room temperature for 3 hours. The reaction mixture was allowed to stand overnight at room temperature, and then insoluble matter was filtered off using a Celite (trade mark) filter aid. The solvent was removed from the filtrate by distillation under reduced pressure. 50 ml of methanol, 25 ml of a 1 N aqueous solution of sodium hydroxide and 10 ml of 2 N aqueous hydrochloric acid were then added to the residue. Air was then blown into the resulting mixture. Five drops of a 1% aqueous solution of ferric chloride were added dropwise to the reaction mixture, and then the mixture was stirred at room temperature for one hour. The reaction mixture was allowed to stand overnight at room temperature, and then the solvent was removed by distillation under reduced pressure. Water was added to the residue, after which it was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulphate. Ethyl acetate was removed from the extract by distillation under reduced pressure, and the residue was subjected to silica gel column chromatography. using 1: 2 and 1 : 1 by volume mixtures of ethyl acetate and hexane as eluent. The solvent was removed from the resulting eluate by distillation under reduced pressure, and 30 ml of toluene were added to the residue. 1 ml was taken from the resulting solution, and the solvent was removed by distillation under reduced pressure, to give 0.13 g of the title compound as a yellow oil having an Rf value of 0.39 (silica gel thin layer chromatography; using a 1 : 1 by volume mixture of ethyl acetate and hexane as the eluent).

PREPARATION 2

6-(1,2-Dithiolan-3-yl)hexanoic acid (Compound No. 1-1467)

[0182]



[0183] 30 ml of water and 60 ml of aqueous hydrochloric acid were added to 7.16 g of 6-(2-oxo-1,3-dithian-4-yl) hexanenitrile, and the mixture was heated under reflux for 5 hours. The reaction mixture was then left to stand at room temperature overnight, after which it was heated under reflux for 2 hours and 30 minutes. The solvent was then removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue, which was then extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the extraction solution by evaporation under reduced pressure, and 150 ml of a 1 N aqueous solution of sodium hydroxide, 40 ml of 2 N aqueous hydrochloric acid and 10 drops of a 1% w/v aqueous solution of ferric chloride were added to the residue. The mixture was then stirred at room temperature for 2 hours and 30 minutes while air was blown through it. The solvent was removed from the reaction mixture by evaporation under reduced pressure, and water was added to the residue, after which it was washed with ethyl acetate. The aqueous layer was neutralized by the addition of 2 N aqueous hydrochloric acid, and ethyl acetate was added to the solution. The aqueous layer (a) and ethyl acetate layer were then separated from the mixture.

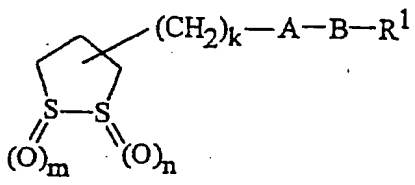
[0184] The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the extraction solution by evaporation under reduced pressure. and the residue was subjected to silica gel column chromatography. using a 1 : 1 by volume mixture of ethyl acetate and hexane as the eluent. The solvent was removed from the eluate by evaporation under reduced pressure, and the residue was dissolved in 40 ml of toluene.

[0185] The ethyl acetate was evaporated from the ethyl acetate layer liberated from the above aqueous layer (a), and 90 ml of a 1 N aqueous solution of sodium hydroxide. 17 ml of 2 N aqueous hydrochloric acid and 5 drops of a 1% w/v aqueous solution of ferric chloride were added to the residue, and then the mixture was stirred at room temperature for 1 hour while air was blown through the mixture. The reaction mixture was left to stand at room temperature overnight, and the solvent was removed from the reaction mixture by evaporation under reduced pressure. Water was added to the residue, and the mixture was washed with ethyl acetate. The aqueous layer was neutralized by the addition of 2 N aqueous hydrochloric acid and extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The extraction solution was combined with the above-mentioned toluene solution, and the solvent was removed from the solution by evaporation under reduced pressure . The residue was subjected to reverse phase preparative silica gel column chromatography, using 2 :

3, 1 : 1 and 3 : 2 by volume mixtures of acetonitrile and water as eluent, and acetonitrile was removed from the solution by evaporation under reduced pressure, after which the residue was extracted with ethyl acetate. The extraction solution was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The ethyl acetate was removed from the extraction solution by evaporation under reduced pressure, and the residue was dissolved in 50 ml of toluene. The toluene was evaporated from 2 ml of the resulting toluene solution, and the residue was dissolved in dioxane and then lyophilised, to obtain 69 mg of the title compound as a yellow oil having an Rf value of 0.39 (silica gel thin layer chromatography; using a 1 : 1 by volume mixture of ethyl acetate and hexane as developing solvent).

Claims

1. Compounds of formula (I):



(I)

in which:

one of m and n represents 0, and the other represents 0, 1 or 2;
k represents 0 or an integer of from 1 to 12;
A represents a group of formula $-CON(R^2)SO_2-$, in which R^2 represents

a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms, an aralkyl group defined below the aryl moiety of which may optionally be substituted by from 1 to 3 of substituents β defined below, an acyl group defined below,
or one of substituents α defined below;

B represents a single bond, or a group of formula $-N(R^5)-$ or $-N(R^6)N(R^5)-$
in which R^5 and R^6 are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms, an aralkyl group defined below the aryl moiety of which may optionally be substituted by from 1 to 3 of substituents β defined below, an acyl group defined below, or one of substituents α defined below, or R^5, together with R^1 and the nitrogen atom to which they are bonded, may form a heterocyclic ring having from 5 to 7 ring atoms defined below;
R^1 represents:

a hydrogen atom,
one of substituents α, defined below, or
an alkyl group having from 1 to 12 carbon atoms which is unsubstituted or is substituted by from 1 to 3 of substituents α defined below and/or substituents γ defined below or such a substituted or unsubstituted alkyl group in which the carbon chain is interrupted by an oxygen atom and/or a sulfur atom,
or, where B represents a single bond or a group of formula $-N(R^5)-$ [in which R^5 is as defined above], R^1 may represent a hydroxy group or a group of formula $-OR^7$ (in which R^7 represents a lower alkyl group defined below, a lower alkenyl group defined below, an aralkyl group defined below of which the aryl moiety may optionally be substituted by from 1 to 3 of substituents β defined below, or one of substituents α);

Substituents α are selected from aryl groups defined below, heterocyclic groups defined below, aryl groups defined below substituted with from 1 to 3 of substituents β, and heterocyclic groups defined below substituted with from 1 to 3 of substituents β;
Substituents β are selected from lower alkyl groups defined below, halogenated lower alkyl groups defined below, lower alkoxy groups defined below, lower alkylthio groups defined below, hydroxy groups, carboxy

groups, optionally-substituted carbamoyl groups defined below, lower alkoxycarbonyl groups defined below, halogen atoms, nitro groups, amine residues defined below, sulfo groups, sulfamoyl groups, cyano groups, and hydroxy-substituted lower alkyl groups defined below;

Substituents γ are selected from lower alkoxy groups defined below, lower alkylthio groups defined below, hydroxy groups, nitrooxy groups, carboxy groups, lower alkoxycarbonyl groups defined below, halogen atoms, sulfo groups, sulfamoyl groups, amine residues defined below, and optionally-substituted carbamoyl groups defined below;

and pharmaceutically acceptable salts thereof;

the aryl groups referred to in the definition of substituents α are carbocyclic aromatic hydrocarbons having from 6 to 14 ring carbon atoms in one or more aromatic carbocyclic rings which may be fused to a cycloalkyl group having from 3 to 10 ring carbon atoms;

the aralkyl groups referred to in the definitions of R^2, R^5, R^6 and R^7 are alkyl groups having from 1 to 6 carbon atoms which are substituted by from 1 to 3 aryl groups defined above;

the acyl groups referred to in the definitions of R^2, R^5 and R^6 are selected from the group consisting of alkylcarbonyl groups having from 1 to 30 carbon atoms, halogenated alkylcarbonyl groups having from 2 to 6 carbon atoms, alkoxyalkylcarbonyl groups in which each of the alkoxy and alkyl moieties has from 1 to 4 carbon atoms, unsaturated alkylcarbonyl groups having from 3 to 6 carbon atoms, arylcarbonyl groups in which the aryl moiety is as defined above, halogenated arylcarbonyl groups in which the aryl moiety is as defined above, (C_{1-6}) alkyl-substituted arylcarbonyl groups in which the aryl moiety is as defined above, hydroxy-substituted arylcarbonyl groups in which the aryl moiety is as defined above, (C_{1-6}) alkoxy-substituted arylcarbonyl groups in which the aryl moiety is as defined above, nitro-substituted arylcarbonyl groups in which the aryl moiety is as defined above, lower alkoxycarbonyl-substituted arylcarbonyl groups in which the aryl moiety is as defined above and the alkoxycarbonyl substituents have from 2 to 7 carbon atoms, aryl-substituted arylcarbonyl groups in which each aryl moiety is as defined above, alkoxycarbonyl groups having from 2 to 7 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms in which the alkoxy moiety is substituted with a halogen atom or a tri-(C_{1-6}) alkyl silyl group, aralkylcarbonyl groups in which the alkyl moiety has from 1 to 6 carbon atoms and the aryl moiety is as defined above and may optionally be substituted by 1 or 2 alkoxy groups having from 1 to 6 carbon atoms or nitro groups, lower alkanesulphonyl groups in which the lower alkyl moiety has from 1 to 6 carbon atoms, halogenated lower alkanesulphonyl groups in which the lower alkyl moiety has from 1 to 6 carbon atoms and arylsulphonyl groups in which the aryl moiety is as defined above;

the 5- to 7-membered heterocyclic rings which may be formed from a combination of R^1, R^5 and the nitrogen atom to which they are attached have from 1 to 3 sulphur and/or oxygen and/or nitrogen atoms of which at least one must be a nitrogen atom, said groups being optionally substituted by 1 or 2 oxygen atoms and/or 1 to 3 of substituents β defined above, and further optionally being fused with a carbocyclic or heterocyclic group having from 3 to 6 ring atoms;

the lower alkyl groups referred to in the definitions of R^7 and substituents β are straight or branched chain groups having from 1 to 6 carbon atoms;

the lower alkenyl groups referred to in the definition of R^7 are straight or branched chain groups having from 2 to 6 carbon atoms;

the heterocyclic groups referred to in the definition of substituents α have from 5 to 7 ring atoms of which from 1 to 3 are sulphur and/or oxygen and/or nitrogen atoms, said groups being saturated or unsaturated, optionally being substituted by 1 or 2 oxygen and/or sulphur atoms, and further optionally being fused with a carbocyclic or heterocyclic group having from 3 to 6 ring atoms;

the halogenated lower alkyl groups referred to in the definition of substituents β comprise a lower alkyl group as defined above which is substitituted by 1 or more halogen atoms;

the lower alkoxy groups referred to in the definitions of substituents β and substituents γ are straight or branched chain groups having from 1 to 6 carbon atoms;

the lower alkylthio groups referred to in the definitions of substituents β and substituents γ are straight or branched chain groups having from 1 to 6 carbon atoms;

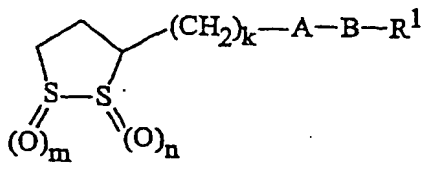
the amine residues referred to in the definitions of substituents β and substituents γ are groups of formula $-NR^aR^b$ wherein R^a and R^b are the same or different and each represents a hydrogen atom, a lower alkyl group as defined above, a cycloalkyl group having from 3 to 8 ring carbon atoms, an aryl group as defined above, a heterocyclic group as defined above, or R^a and R^b together with the nitrogen atom to which they are attached represent a 5- to 7-membered nitrogen-containing heterocyclic group as defined above;

the optionally-substituted carbamoyl groups referred to in the defintions of substituents β and substituents γ are groups of formula $-CONR^{a'}R^{b'}$ wherein $R^{a'}$ and $R^{b'}$ are the same or different and each represents any of the atoms or groups represented by R^a and R^b defined above or one of $R^{a'}$ and $R^{b'}$ represents a hydrogen atom and the other represents an acyl group as defined above or an aminosulphonyl group;

the lower alkoxycarbonyl groups referred to in the definitions of substituents β and substituents γ comprise a carbonyl group which is substituted by a straight or branched chain alkoxy group having from 1 to 6 carbon atoms; and

the hydroxy-substituted lower alkyl groups referred to in the definitions of substituents β and substituents γ are lower alkyl groups as defined above which are substituted by 1 or more hydroxy groups.

2. A compound according to Claim 1, represented by the formula (I'):



(I')

(in which A, B, R^1, k, m and n are as defined in Claim 1) and salts thereof.

3. A compound according to Claim 1 or Claim 2, in which one of m and n is 0, and the other is 0 or 1.

4. A compound according to any one of Claims 1 to 3, in which k is 0 or an integer of from 1 to 8.

5. A compound according to any one of Claims 1 to 4, in which R^1 represents a heterocyclic group as defined in Claim 1, an alkyl group having from 1 to 12 carbon atoms which is unsubstituted or is substituted by from 1 to 3 of substituents α as defined in Claim 1 and substituents γ as defined in Claim 1 or such a substituted or unsubstituted alkyl group in which the carbon chain is interrupted by an oxygen atom and/or a sulfur atom.

6. A compound according to any one of Claims 1 to 4, in which R^1 represents a hydroxy group or an alkoxy group having from 1 to 5 carbon atoms.

7. A compound according to any one of Claims 1 to 6, in which A represents a group of formula $-CON(R^2)SO_2-$ in which R^2 represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or a benzyl group.

8. A compound according to any one of Claims 1 to 7, in which B represents a single bond, or a group of formula $-N(R^5)-$ or $-N(R^5)N(R^6)-$, in which R^5 and R^6 are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or a benzyl group.

9. A compound according to Claim 1 or Claim 2, in which:

one of m and n is 0, and the other is 0 or 1;

k is 0 or an integer of from 1 to 8;

R^1 represents a heterocyclic group as defined in Claim 1, a hydroxy group, an alkoxy group having from 1 to 5 carbon atoms, an alkyl group having from 1 to 12 carbon atoms which is unsubstituted or is substituted by from 1 to 3 of substituents α as defined in Claim 1 and/or substituents γ as defined in Claim 1 or such a substituted or unsubstituted alkyl group in which the carbon chain is interrupted by an oxygen atom and/or a sulfur atom;

A represents a group of formula $-CON(R^2)SO_2-$, in which R^2 represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or a benzyl group; and

B represents a single bond, or a group of formula $-N(R^5)-$ or $-N(R^5)N(R^6)-$, in which R^5 and R^6 are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or a benzyl group.

10. A compound according to Claim 1 or Claim 2, in which both of m and n are 0.

11. A compound according to any one of Claims 1, 2 and 10, in which k is an integer of from 2 to 6.

12. A compound according to any one of Claims 1, 2, 10 and 11, in which R^1 represents an alkyl group having from 1

to 5 carbon atoms, an alkoxycarbonylalkyl group having from 3 to 8 carbon atoms, a carboxyalkyl group having from 2 to 7 carbon atoms, a hydroxyalkyl group having from 2 to 5 carbon atoms, a heterocyclic group as defined in Claim 1, an alkoxy group having from 1 to 5 carbon atoms or a hydroxy group.

13. A compound according to any one of Claims 1, 2 and 10 to 12, in which A represents a group of formula -CON(R^2)SO_2 -, in which R^2 represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms.

14. A compound according to any one of Claims 1, 2 and 10 to 13, in which B represents a single bond, or a group of formula -N(R^5)- or -N(R^5)N(R^6)-, in which R^5 and R^6 are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms.

15. A compound according to Claim 1 or Claim 2, in which:

both of m and n are 0;
k is an integer of from 2 to 6;
R^1 represents an alkyl group having from 1 to 5 carbon atoms, an alkoxycarbonylalkyl group having from 3 to 8 carbon atoms, a carboxyalkyl group having from 2 to 7 carbon atoms, a hydroxyalkyl group having from 2 to 5 carbon atoms, a heterocyclic group as defined in Claim 1, an alkoxy group having from 1 to 5 carbon atoms or a hydroxy group;
A represents a group of formula -CON(R^2)SO_2-, in which R^2 represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms; and
B represents a single bond, or a group of formula -N(R^5)- or -N(R^5)N(R^6)-, in which R^5 and R^6 are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms.

16. A compound according to Claim 1 or Claim 2, in which k is 4 or 5.

17. A compound according to any one of Claims 1,2 and 16, in which R^1 represents an alkyl group having from 1 to 5 carbon atoms, an alkoxycarbonylalkyl group having from 3 to 8 carbon atoms, a carboxyalkyl group having from 2 to 7 carbon atoms, a hydroxyalkyl group having from 2 to 5 carbon atoms, a heterocyclic group as defined in Claim 1 or an alkoxy group having from 1 to 5 carbon atoms.

18. A compound according to any one of Claims 1, 2, 16 and 17, in which A represents a group of formula -CONHSO_2-, or -CONCH_3SO_2-.

19. A compound according to any one of Claims 1, 2 and 16 to 18, in which B represents a single bond, or a group of formula -NH-, -NCH_3- or -NHNCH_3-.

20. A compound according to Claim 1 or Claim 2, in which:

both of m and n are 0;
k is 4 or 5;
R^1 represents an alkyl group having from 1 to 5 carbon atoms, an alkoxycarbonylalkyl group having from 3 to 8 carbon atoms, a carboxyalkyl group having from 2 to 7 carbon atoms, a hydroxyalkyl group having from 2 to 5 carbon atoms, a heterocyclic group as defined in Claim 1 or an alkoxy group having from 1 to 5 carbon atoms;
A represents a group of formula -CONHSO_2- or -CONCH_3SO_2-; and B represents a single bond, or a group of formula -NH-, -NCH_3- or -NHNCH_3-.

21. N-[5-(1,2-Dithiolan-3-yl)pentanoyl]methanesulphonamide and pharmaceutically acceptable salts thereof.

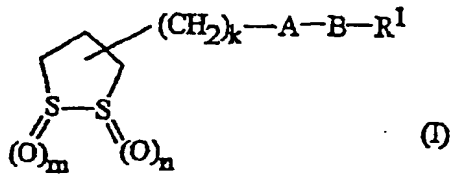
22. The use of a compound according to any one of Claims 1 to 21 for the manufacture of a medicament for enhancing the activity of glutathione reductase in a mammal.

23. The use of a compound according to any one of Claims 1 to 21 for the manufacture of a medicament for the treatment or prevention of cataract in a mammal.

24. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 21 in admixture with a pharmaceutically acceptable diluent or carrier.

Patentansprüche

1. Verbindungen der Formel (I):



(I)

worin:

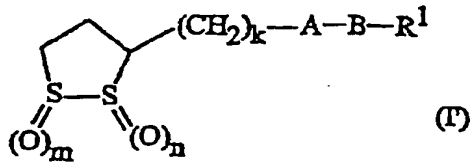
entweder m oder n 0 ist und das jeweils andere 0, 1 oder 2 ist,
k 0 oder eine ganze Zahl von 1 bis 12 ist,
A eine Gruppe der Formel $-CON(R^2)SO_2-$ ist, worin R^2
ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen, eine nachstehend definierte Aralkylgruppe, wobei der Arylrest gegebenenfalls mit 1 bis 3 der nachstehend definierten Substituenten β substituiert sein kann, eine nachstehend definierte Acylgruppe oder einen der nachstehend definierten Substituenten α darstellt,
B eine Einfachbindung oder eine Gruppe der Formel $-N(R^5)-$ oder $-N(R^6)N(R^5)-$ darstellt,
worin R^5 und R^6 gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen, eine nachstehend definierte Aralkylgruppe, wobei der Arylrest gegebenenfalls mit 1 bis 3 der nachstehend definierten Substituenten β substituiert sein kann, eine nachstehend definierte Acylgruppe oder einen der nachstehend definierten Substituenten α darstellen, oder R^5 zusammen mit R^1 und dem Stickstoffatom, an das sie gebunden sind, einen heterocyclischen Ring mit 5 bis 7 der nachstehend definierten Ringatome bilden kann,
R^1 darstellt:

ein Wasserstoffatom,
einen der nachstehend definierten Substituenten α oder eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen, die unsubstituiert oder mit 1 bis 3 der nachstehend definierten Substituenten α und/oder der nachstehend definierten Substituenten γ substituiert ist, oder eine solche substituierte oder unsubstituierte Alkylgruppe, worin die Kohlenstoffkette durch ein Sauerstoffatom und/oder Schwefelatom unterbrochen ist, oder, wenn B eine Einfachbindung oder eine Gruppe der Formel $-N(R^5)-$ [worin R^5 wie vorstehend definiert ist] darstellt, R^1 eine Hydroxygruppe oder eine Gruppe der Formel $-OR^7$ darstellen kann (worin R^7 eine nachstehend definierte Niederalkylgruppe, eine nachstehend definierte Niederalkenylgruppe, eine nachstehend definierte Aralkylgruppe, wobei der Arylrest gegebenenfalls mit 1 bis 3 der nachstehend definierten Substituenten β substituiert sein kann, oder einen der Substituenten α darstellt),

wobei die Substituenten α aus den nachstehend definierten Arylgruppen, den nachstehend definierten heterocyclischen Gruppen, den nachstehend definierten Arylgruppen, die mit 1 bis 3 Substituenten β substituiert sind, und den nachstehend definierten heterocyclischen Gruppen, die mit 1 bis 3 Substituenten β substituiert sind, ausgewählt sind,
die Substituenten β unter den nachstehend definierten Niederalkylgruppen, den nachstehend definierten halogenierten Niederalkylgruppen, den nachstehend definierten Niederalkoxygruppen, den nachstehend definierten Niederalkylthiogruppen, Hydroxygruppen, Carboxygruppen, den nachstehend definierten gegebenenfalls substituierten Carbamoylgruppen, den nachstehend definierten Niederalkoxycarbonylgruppen, Halogenatomen, Nitrogruppen, den nachstehend definierten Aminresten, Sulfogruppen, Sulfamoylgruppen, Cyangruppen und den nachstehend definierten hydroxysubstituierten Niederalkylgruppen ausgewählt sind, die Substituenten γ unter den nachstehend definierten Niederalkoxygruppen, den nachstehend definierten Niederalkylthiogruppen, Hydroxygruppen, Nitrooxygruppen, Carboxygruppen, den nachstehend definierten Niederalkoxycarbonylgruppen, Halogenatomen, Sulfogruppen, Sulfamoylgruppen, den nachstehend definierten Aminresten und den nachstehend definierten gegebenenfalls substituierten Carbamoylgruppen ausgewählt sind,

und pharmazeutisch geeignete Salze davon,
wobei die inder Definition der Substituenten α genannten Arylgruppen carbocyclische aromatische Kohlenwasserstoffe mit 6 bis 14 Ringkohlenstoffatomen in einem oder mehr aromatischen carbocyclischen Ringen sind, die an eine Cycloalkylgruppe mit 3 bis 10 Ringkohlenstoffatomen kondensiert sein können,
die in den Definitionen von R^2, R^5, R^6 und R^7 genannten Aralkylgruppen Alkylgruppen mit 1 bis 6 Kohlenstoffatomen sind, die mit 1 bis 3 der vorstehend definierten Arylgruppen substituiert sind,
die in den Definitionen von R^2, R^5 und R^6 genannten Acylgruppen aus der Gruppe ausgewählt sind, die aus Alkylcarbonylgruppen mit 1 bis 30 Kohlenstoffatomen, halogenierten Alkylcarbonylgruppen mit 2 bis 6 Kohlenstoffatomen, Alkoxyalkylcarbonylgruppen, worin jeder der Alkoxyreste und Alkylreste 1 bis 4 Kohlenstoffatome hat, ungesättigten Alkylcarbonylgruppen mit 3 bis 6 Kohlenstoffatomen, Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist, halogenierten Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist, (C_{1-6})-alkylsubstituierten Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist, hydroxysubstituierten Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist, (C_{1-6})-alkoxysubstituierten Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist, nitrosubstituierten Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist, niederalkoxycarbonylsubstituierten Arylcarbonylgruppen, worin der Arylrest wie vorstehend definiert ist und die Alkoxycarbonylsubstituenten 2 bis 7 Kohlenstoffatome haben, arylsubstituierten Arylcarbonylgruppen, worin jeder Arylrest wie vorstehend definiert ist, Alkoxycarbonylgruppen mit 2 bis 7 Kohlenstoffatomen, Alkoxycarbonylgruppen mit 2 bis 7 Kohlenstoffatomen, worin der Alkoxyrest mit einem Halogenatom oder einer Tri(C_{1-6})-Alkylsilylgruppe substituiert ist, Aralkylcarbonylgruppen, worin der Alkylrest 1 bis 6 Kohlenstoffatome hat und der Arylrest wie vorstehend definiert ist und gegebenenfalls mit 1 oder 2 Alkoxygruppen mit 1 bis 6 Kohlenstoffatomen oder Nitrogruppen substituiert sein kann, Niederalkansulfonylgruppen, worin der Niederalkylrest 1 bis 6 Kohlenstoffatome hat, halogenierten Niederalkansulfonylgruppen, worin der Niederalkylrest 1 bis 6 Kohlenstoffatome hat, und Arylsulfonylgruppen besteht, worin der Arylrest wie vorstehend definiert ist, die 5- bis 7-gliedrigen heterocyclischen Ringe, die aus einer Kombination von R^1, R^5 und dem Stickstoffatom, an das sie gebunden sind, gebildet werden, 1 bis 3 Schwefel- und/oder Sauerstoff- und/oder Stickstoffatome haben, von denen mindestens eins ein Stickstoffatom ist, wobei die Gruppen gegebenenfalls mit 1 oder 2 Sauerstoffatomen und/oder 1 bis 3 der vorstehend definierten Substituenten β substituiert sind und außerdem gegebenenfalls mit einer carbocyclischen oder heterocyclischen Gruppe mit 3 bis 6 Ringatomen kondensiert sind,
die in den Definitionen von R^7 und den Substituenten β genannten Niederalkylgruppen geradkettige oder verzweigte Gruppen mit 1 bis 6 Kohlenstoffatomen sind,
die in der Definition von R^7 genannten Niederalkenylgruppen geradkettige oder verzweigte Gruppen mit 2 bis 6 Kohlenstoffatomen sind,
die in der Definition der Substituenten α genannten heterocyclischen Gruppen 5 bis 7 Ringatome haben, von denen 1 bis 3 Schwefel- und/oder Sauerstoff- und/oder Stickstoffatome sind, wobei die Gruppen gesättigt oder ungesättigt sind und gegebenenfalls mit 1 oder 2 Sauerstoff- und/oder Schwefelatomen substituiert sind und außerdem gegebenenfalls an eine carbocyclische oder heterocyclische Gruppe mit 3 bis 6 Ringatomen kondensiert sind,
die in der Definition der Substituenten β genannten halogenierten Niederalkylgruppen eine vorstehend definierte Niederalkylgruppe umfassen, die mit einem oder mehr Halogenatomen substituiert ist,
die in den Definitionen der Substituenten β und der Substituenten γ genannten Niederalkoxygruppen geradkettige oder verzweigte Gruppen mit 1 bis 6 Kohlenstoffatomen sind,
die in den Definitionen der Substituenten β und der Substituenten γ genannten Niederalkylthiogruppen geradkettige oder verzweigte Gruppen mit 1 bis 6 Kohlenstoffatomen sind,
die in den Definitionen der Substituenten β und der Substituenten γ genannten Aminreste Gruppen der Formel $-NR^aR^b$ sind, worin R^a und R^b gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom, eine vorstehend definierte Niederalkylgruppe, eine Cycloalkylgruppe mit 3 bis 8 Ringatomen, eine vorstehend definierte Arylgruppe oder eine vorstehend definierte heterocyclische Gruppe darstellen, oder R^a und R^b zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine vorstehend definierte 5- bis 7-gliedrige Stickstoff enthaltende heterocyclische Gruppe darstellen,
die in den Definitionen der Substituenten β und Substituenten γ genannten gegebenenfalls substituierten Carbamoylgruppen Gruppen der Formel $-CONR^{a'}R^{b'}$ sind, worin $R^{a'}$ und $R^{b'}$ gleich oder unterschiedlich sind und jeweils die Atome oder Gruppen, die durch die vorstehend definierten R^a und R^b dargestellt sind, darstellen, oder einer der Substituenten $R^{a'}$ und $R^{b'}$ ein Wasserstoffatom und der andere eine vorstehend definierte Acylgruppe darstellt,
die in den Definitionen der Substituenten β und der Substituenten γ genannten Niederalkoxycarbonylgruppen eine Carbonylgruppe enthalten, die mit einer geradkettigen oder verzweigten Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen substituiert ist, und
die in den Definitionen der Substituenten β und Substituenten γ genannten hydroxysubstituierten Niederalkylgruppen vorstehend definierte Niederalkylgruppen sind, die mit 1 oder mehr Hydroxygruppen substituiert sind.

2. Verbindung nach Anspruch 1, dargestellt durch die Formel (I'):



(I')

(worin A, B, R^1, k, m und n wie in Anspruch 1 definiert sind) und Salze davon.

3. Verbindung nach Anspruch 1 oder 2, worin entweder m oder n 0 ist und das andere 0 oder 1 ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, worin k 0 oder eine ganze Zahl von 1 bis 8 ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, worin R^1 eine in Anspruch 1 definierte heterocyclische Gruppe, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen, die unsubstituiert oder mit 1 bis 3 der in Anspruch 1 definierten Substituenten α und der in Anspruch 1 definierten Substituenten γ substituiert sind, und eine solche substituierte oder unsubstituierte Alkylgruppe, worin die Kohlenstoffkette durch ein Sauerstoffatom und/oder Schwefelatom unterbrochen ist.

6. Verbindung nach einem der Ansprüche 1 bis 4, worin R^1 eine Hydroxygruppe oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen darstellt.

7. Verbindung nach einem der Ansprüche 1 bis 6, worin A eine Gruppe der Formel $-CON(R^2)SO_2-$ darstellt, worin R^2 ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen oder eine Benzylgruppe darstellt.

8. Verbindung nach einem der Ansprüche 1 bis 7, worin B eine Einfachbindung oder eine Gruppe der Formel $-N(R^5)-$ oder $-N(R^5)N(R^6)-$ ist, worin R^5 und R^6 gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen oder eine Benzylgruppe sind.

9. Verbindung nach Anspruch 1 oder 2, worin:

entweder m oder n 0 ist und das andere 0 oder 1 ist,
k 0 oder eine ganze Zahl von 1 bis 8 ist,
R^1 eine in Anspruch 1 definierte heterocyclische Gruppe, eine Hydroxygruppe, eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen, die unsubstituiert oder mit 1 bis 3 der in Anspruch 1 definierten Substituenten α und/oder der in Anspruch 1 definierten Substituenten γ substituiert ist, oder eine solche substituierte oder unsubstituierte Alkylgruppe, worin die Kohlenstoffkette durch ein Sauerstoffatom und/oder Schwefelatom unterbrochen ist,
A eine Gruppe der Formel $-CON(R^2)SO_2-$ ist, worin R^2 ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen oder eine Benzylgruppe darstellt, und
B eine Einfachbindung oder eine Gruppe der Formel $-N(R^5)-$ oder $-N(R^5)N(R^6)-$ darstellt, worin R^5 und R^6 gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen oder eine Benzylgruppe darstellen.

10. Verbindung nach Anspruch 1 oder 2, worin sowohl m als auch n 0 ist.

11. Verbindung nach einem der Ansprüche 1, 2 und 10, worin k eine ganze Zahl von 2 bis 6 ist.

12. Verbindung nach einem der Ansprüche 1, 2, 10 und 11, worin R^1 eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkoxycarbonylalkylgruppe mit 3 bis 8 Kohlenstoffatomen, eine Carboxyalkylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Hydroxyalkylgruppe mit 2 bis 5 Kohlenstoffatomen, eine in Anspruch 1 definierte heterocyclische Gruppe, eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen oder eine Hydroxygruppe darstellt.

13. Verbindung nach einem der Ansprüche 1, 2 und 10 bis 12, worin A eine Gruppe der Formel $-CON(R^2)SO_2-$ darstellt, worin R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen darstellt.

14. Verbindung nach einem der Ansprüche 1, 2 und 10 bis 13, worin B eine Einfachbindung oder eine Gruppe der Formel $-N(R^5)-$ oder $-N(R^5)N(R^6)$ darstellt, worin R^5 und R^6 gleich oder unterschiedlich und und jeweils ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen darstellen.

15. Verbindung nach Anspruch 1 oder 2, worin:

sowohl m als auch n 0 ist,
k eine ganze Zahl von 2 bis 6 ist,
R^1 eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkoxycarbonylalkylgruppe mit 3 bis 8 Kohlenstoffatomen, eine Carboxyalkylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Hydroxyalkylgruppe mit 2 bis 5 Kohlenstoffatomen, eine in Anspruch 1 definierte heterocyclische Gruppe, eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen oder eine Hydroxygruppe darstellt,
A eine Gruppe der Formel $-CON(R^2)SO_2-$ darstellt, worin R^2 ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen darstellt, und
B eine Einfachbindung oder eine Gruppe der Formel $-N(R^5)-$ oder $-N(R^5)N(R^6)-$ darstellt, worin R^5 und R^6 gleich oder unterschiedlich sind und jeweils ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 12 Kohlenstoffatomen darstellen.

16. Verbindung nach Anspruch 1 oder 2, worin k 4 oder 5 ist.

17. Verbindung nach einem der Ansprüche 1, 2 und 16, worin R^1 eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkoxycarbonylalkylgruppe mit 3 bis 8 Kohlenstoffatomen, eine Carboxyalkylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Hydroxyalkylgruppe mit 2 bis 5 Kohlenstoffatomen, eine in Anspruch 1 definierte heterocyclische Gruppe oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen darstellt.

18. Verbindung nach einem der Ansprüche 1, 2, 16 und 17, worin A eine Gruppe der Formel $-CONHSO_2-$ oder $-CONCH_3SO_2-$ darstellt.

19. Verbindung nach einem der Ansprüche 1, 2 und 16 bis 18, worin B eine Einfachbindung oder eine Gruppe der Formel -NH-, $-NCH_3-$ oder $-NHNCH_3-$ darstellt.

20. Verbindung nach Anspruch 1 oder 2, worin:

sowohl m als auch n 0 ist,
k 4 oder 5 ist,
R^1 eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkoxycarbonylalkylgruppe mit 3 bis 8 Kohlenstoffatomen, eine Carboxyalkylgruppe mit 2 bis 7 Kohlenstoffatomen, eine Hydroxyalkylgruppe mit 2 bis 5 Kohlenstoffatomen, eine in Anspruch 1 definierte heterocyclische Gruppe oder eine Alkoxygruppe mit 1 bis 5 Kohlenstoffatomen darstellt,
A eine Gruppe der $-CONHSO_2-$ oder $-CONCH_3SO_2-$ darstellt und
B eine Einfachbindung oder eine Gruppe der Formel -NH-, $-NCH_3-$ oder $-NHNCH_3-$ darstellt.

21. N-[5-(1,2-Dithiolan-3-yl)pentanoyl]methansulfonamid und pharmazeutisch geeignete Salze davon.

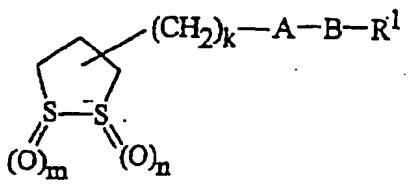
22. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 21 für die Herstellung eines Arzneimittels zum Erhöhen der Aktivität von Glutathionreduktase in einem Säuger.

23. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 21 für die Herstellung eines Arzneimittels zur Behandlung oder Verhinderung eines Katarakts in einem Säuger.

24. Arzneimittelzusammensetzung, welche eine Verbindung nach einem der Ansprüche 1 bis 21 im Gemisch mit einem pharmazeutisch geeigneten Verdünnungsmittel oder Träger enthält.

Revendications

1. Composés de formule (I) :



(I)

dans laquelle :

l'un de m et n représente 0 et l'autre représente 0, 1 ou 2 ;
k représente 0 ou un nombre entier de 1 à 12 ;
A représente un groupe de formule $-CON(R^2)SO_2-$ où R^2 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 12 atomes de carbone, un groupe aralkyle défini ci-dessus dont la portion aryle peut facultativement être substituée par 1 à 3 des substituants β définis ci-dessous, un groupe acyle défini ci-dessous, ou l'un des substituants α définis ci-dessous ;
B représente une liaison simple, ou un groupe de formule $-N(R^5)-$ ou $-N(R^6)N(R^5)-$ où R^5 et R^6 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 12 atomes de carbone, un groupe aralkyle défini ci-dessous dont la portion aryle peut facultativement être substituée par 1 à 3 des substituants β définis ci-dessous, un groupe acyle défini ci-dessous, ou l'un des substituants α définis ci-dessous,
ou bien R^5, avec R^1 et l'atome d'azote auquel ils sont liés, peut former un hétérocycle ayant 5 à 7 atomes cycliques définis ci-dessous;
R^1 représente :

un atome d'hydrogène,
l'un des substituants α définis ci-dessous, ou
un groupe alkyle ayant 1 à 12 atomes de carbone qui n'est pas substitué ou est substitué par 1 à 3 substituants α définis ci-dessous et/ou substituants γ définis ci-dessous ou un tel groupe alkyle substitué ou non substitué dans lequel la chaîne carbonée est interrompue par un atome d'oxygène et/ou un atome de soufre,
ou bien, lorsque B représente une liaison simple ou un groupe de formule $-N(R^5)-$ [où R^5 est tel que défini ci-dessus], R^1 peut représenter un groupe hydroxyle ou un groupe de formule $-OR^7$ (où R^7 représente un groupe alkyle inférieur défini ci-dessous, un groupe alcényle inférieur défini ci-dessous, un groupe aralkyle défini ci-dessous dont la portion aryle peut facultativement être substituée par 1 à 3 substituants β définis ci-dessous, ou l'un des substituants α) ;

les substituants α sont choisis parmi les groupes aryle définis ci-dessous, les groupes hétérocycliques définis ci-dessous, les groupes aryle définis ci-dessous substitués par 1 à 3 des substituants β, et les groupes hétérocycliques définis ci-dessous substitués par 1 à 3 des substituants β ;

les substituants β sont choisis parmi les groupes alkyle inférieurs définis ci-dessous, les groupes alkyle inférieurs halogénés définis ci-dessous, les groupes alcoxy inférieurs définis ci-dessous, les groupes alkylthio inférieurs défini ci-dessous, les groupes hydroxyle, les groupes carboxy, les groupes carbamoyle facultativement substitués définis ci-dessous, les groupes (alcoxy inférieur)carbonyle définis ci-dessous, les atomes d'halogène, les groupes nitro, les résidus d'amine définis ci-dessous, les groupes sulfo, les groupes sulfamoyle, les groupes cyano et les groupes alkyle inférieurs à substitution hydroxyle définis ci-dessous ;

les substituants γ sont choisis parmi les groupes alcoxy inférieurs définis ci-dessous, les groupes alkylthio inférieurs définis ci-dessous, les groupes hydroxyle, les groupes nitroxy, les groupes carboxy, les groupes (alcoxy inférieur)carbonyle définis ci-dessous, les atomes d'halogène, les groupes sulfo, les groupes sulfamoyle, les résidus d'aminé définis ci-dessous et les groupes carbamoyle facultativement substitués définis ci-dessous ; et leurs sels pharmaceutiquement acceptables ;

les groupes aryle visés dans la définition des substituants α sont des hydrocarbures aromatiques carbocycliques ayant 6 à 14 atomes de carbone cycliques dans un ou plusieurs carbocycles aromatiques qui peuvent être

condensés à un groupe cycloalkyle ayant 3 à 10 atomes de carbone cycliques ;

les groupes aralkyle visés dans les définitions de R^2, R^5, R^6 et R^7 sont des groupes alkyle ayant 1 à 6 atomes de carbone qui sont substitués par 1 à 3 groupes aryle définis ci-dessus ;

les groupes acyle visés dans les définitions de R^2, R^5 et R^6 sont choisis dans la classe formée par les groupes alkylcarbonyle ayant 1 à 30 atomes de carbone, les groupes alkylcarbonyle halogènes ayant 2 à 6 atomes de carbone-, les groupes alcoxyalkylcarbonyle dans lesquels chacune des portions alcoxy et alkyle compte 1 à 4 atomes de carbone, les groupes alkylcarbonyle insaturés ayant 3 à 6 atomes de carbone, les groupes arylcarbonyle dans lesquels la portion aryle est telle que définie ci-dessus, les groupes arylcarbonyle halogénés dans lesquels la portion aryle est telle que définie ci-dessus, les groupes arylcarbonyle à substitution alkyle en C_1-C_6 dans lesquels la portion aryle est telle que définie ci-dessus, les groupes arylcarbonyle à substitution hydroxyle dans lesquels la portion aryle est telle que définie ci-dessus, les groupes arylcarbonyle à substitution alcoxy en C_1-C_6 dans lesquels la portion aryle est telle que définie ci-dessus, les groupes arylcarbonyle à substitution nitro dans lesquels la portion aryle est telle que définie ci-dessus, les groupes arylcarbonyle à substitution (alcoxy inférieur)carbonyle dans lesquels la portion aryle est telle que définie ci-dessus et les substituants alcoxycarbonyle ont 2 à 7 atomes de carbone, les groupes arylcarbonyle à substitution aryle dans lesquels chaque portion aryle est telle que définie ci-dessus, les groupes alcoxycarbonyle ayant 2 à 7 atomes de carbone, les groupes alcoxycarbonyle ayant 2 à 7 atomes de carbone dans lesquels la portion alcoxy est substituée par un atome d'halogène ou un groupe tri(alkyle en C_1-C_6)silyle, les groupes aralkylcarbonyle dans lesquels la portion alkyle compte 1 à 6 atomes de carbone et la portion aryle est telle que définie ci-dessus et peut être facultativement substituée par 1 ou 2 groupes alcoxy ayant 1 à 6 atomes de carbone ou groupes nitro, les groupes (alcane inférieur)-sulfonyle dans lesquels la portion alkyle inférieur compte 1 à 6 atomes de carbone, les groupes (alcane inférieur)-sulfonyle halogénés dans lesquels la portion alkyle inférieur compte 1 à 6 atomes de carbone et les groupes arylsulfonyle dans lesquels la portion aryle est telle que définie ci-dessus ;

les hétérocycles à 5 à 7 chaînons qui peuvent être formés par une combinaison de R^1, R^5 et l'atome d'azote auquel ils sont liés ont 1 à 3 atomes de soufre et/ou d'oxygène et/ou d'azote dont au moins l'un doit être un atome d'azote, lesdits groupes étant facultativement substitués par 1 ou 2 atomes d'oxygène et/ou 1 à 3 substituants β définis ci-dessus, et étant de plus facultativement condensés à un groupe carbocyclique ou hétérocyclique ayant 3 à 6 atomes cycliques ;

les groupes alkyle inférieurs visés dans les définitions de R^7 et des substituants β sont des groupes à chaîne linéaire ou ramifiée ayant 1 à 6 atomes de carbone ;

les groupes alcényle inférieurs visés dans la définition de R^7 sont des groupes à chaîne linéaire ou ramifiée ayant 2 à 6 atomes de carbone ;

les groupes hétérocycliques visés dans la définition des substituants α ont 5 à 7 atomes cycliques dont 1 à 3 sont des atomes de soufre et/ou d'oxygène et/ou d'azote, lesdits groupes étant saturés ou insaturés, étant facultativement substitués par 1 ou 2 atomes d'oxygène et/ou de soufre, et étant de plus facultativement condensés à un groupe carbocyclique ou hétérocyclique ayant 3 à 6 atomes cycliques ;

les groupes alkyle inférieurs halogénés visés dans la définition des substituants β comprennent un groupe alkyle inférieur tel que défini ci-dessus qui est substitué par un ou plusieurs atomes d'halogène ;

les groupes alcoxy inférieurs visés dans la définition des substituants β et des substituants γ sont des groupes à chaîne linéaire ou ramifiée ayant 1 à 6 atomes de carbone ;

les groupes alkylthio inférieurs visés dans les définitions des substituants β et des substituants γ sont des groupes à chaîné linéaire ou ramifiée ayant 1 à 6 atomes de carbone ;

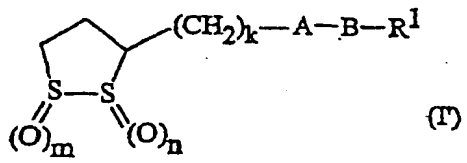
les résidus d'aminé visés dans les définitions des substituants β et des substituants γ sont des groupes de formule $-NR^aR^b$ où R^a et R^b sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle inférieur tel que défini ci-dessus, un groupe cycloalkyle ayant 3 à 8 atomes de carbone cycliques, un groupe aryle tel que défini ci-dessus, un groupe hétérocyclique tel que défini ci-dessus, ou bien R^a et R^b, avec l'atome d'azote auquel ils sont liés, représentent un groupe hétérocyclique azoté à 5 à 7 chaînons tel que défini ci-dessus ;

les groupes carbamoyle facultativement substitués visés dans les définitions des substituants β et des substituants γ sont des groupes de formule $-CONR^{a'}R^{b'}$ où $R^{a'}$ et $R^{b'}$ sont identiques ou différents et représentent chacun n'importe lequel des atomes ou groupes représentés par R^a et R^b définis ci-dessus ou bien l'un de $R^{a'}$ et $R^{b'}$ représente un atome d'hydrogène et l'autre représente un groupe acyle tel que défini ci-dessus ou un groupe aminosulfonyle ;

les groupes (alcoxy inférieur)carbonyle visés dans les définitions des substituants β et des substituants γ comprennent un groupe carbonyle qui est substitué par un groupe alcoxy à chaîne linéaire ou ramifiée ayant 1 à 6 atomes de carbone ; et

les groupes alkyle inférieurs à substitution hydroxyle visés dans les définitions des substituants β et des substituants γ sont les groupes alkyle inférieurs tels que définis ci-dessus qui sont substitués par un ou plusieurs groupes hydroxyle.

2. Composé selon la revendication 1, représenté par la formule (I') :



(I')

(dans laquelle A, B, R^1, k, m et n sont tels que définis dans la revendication 1) et ses sels.

3. Composé selon la revendication 1 ou la revendication 2, dans lequel l'un de m et n est 0 et l'autre est 0 ou 1.

4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel k est 0 ou un nombre entier de 1 à 8.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R^1 représente un groupe hétérocyclique tel que défini dans la revendication 1, un groupe alkyle ayant 1 à 12 atomes de carbone qui n'est pas substitué ou est substitué par 1 à 3 des substituants α tels que définis dans la revendication 1 et des substituants γ tels que définis dans la revendication 1 ou un tel groupe alkyle substitué ou non substitué dans lequel la chaîne carbonée est interrompue par un atome d'oxygène et/ou un atome de soufre.

6. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R^1 représente un groupe hydroxyle ou un groupe alcoxy ayant 1 à 5 atomes de carbone.

7. Composé selon l'une quelconque des revendications 1 à 6, dans lequel A représente un groupe de formule -CON(R^2)SO_2- où R^2 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 12 atomes de carbone ou un groupe benzyle.

8. Composé selon l'une quelconque des revendications 1 à 7, dans lequel B représente une liaison simple ou un groupe de formule -N(R^5)- ou -N(R^5)N(R^6)-, où R^5 et R^6 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 12 atomes de carbone ou un groupe benzyle.

9. Composé selon la revendication 1 ou la revendication 2, dans lequel :

l'un de m et n est 0, et l'autre est 0 ou 1 ;
k est 0 ou un nombre entier de 1 à 8 ;
R^1 représente un groupe hétérocyclique tel que défini dans la revendication 1, un groupe hydroxyle, un groupe alcoxy ayant 1 à 5 atomes de carbone, un groupe alkyle ayant 1 à 12 atomes de carbone qui n'est pas substitué ou est substitué par 1 à 3 des substituants α tels que définis dans la revendication 1 et/ou des substituants γ tels que définis dans la revendication 1 ou un tel groupe alkyle substitué ou non substitué dans lequel la chaîne carbonée est interrompue par un atome d'oxygène et/ou un atome de soufre ;
A représente un groupe de formule -CON(R^2)SO_2- où R^2 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 12 atomes de carbone ou un groupe benzyle ; et
B représente une liaison simple, ou un groupe de formule -N(R5)- ou -N(R^5)N(R^6)-, où R^5 et R^6 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 12 atomes de carbone ou un groupe benzyle.

10. Composé selon la revendication 1 ou la revendication 2, dans lequel m et n sont tous deux 0.

11. Composé selon l'une quelconque des revendications 1, 2 et 10, dans lequel k est un nombre entier de 2 à 6.

12. Composé selon l'une quelconque des revendications 1, 2, 10 et 11, dans lequel R^1 représente un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcoxycarbonylalkyle ayant 3 à 8 atomes de carbone, un groupe carboxyalkyle ayant 2 à 7 atomes de carbone, un groupe hydroxyalkyle ayant 2 à 5 atomes de carbone, un groupe hétérocyclique tel que défini dans la revendication 1, un groupe alcoxy ayant 1 à 5 atomes de carbone ou un groupe hydroxyle.

13. Composé selon l'une quelconque des revendications 1, 2 et 10 à 12, dans lequel A représente un groupe de formule $-CON(R^2)SO_2-$ où R^2 représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 12 atomes de carbone.

14. Composé selon l'une quelconque des revendications 1, 2 et 10 à 13, dans lequel B représente une liaison simple, ou un groupe de formule $-N(R^5)-$ ou $-N(R^5)N(R^6)-$, où R^5 et R^6 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle ayant 1 à 12 atomes de carbone.

15. Composé selon la revendication 1 ou la revendication 2, dans lequel :

m et n sont tous deux 0 ;
k est un nombre entier de 2 à 6 ;
R^1 représente un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcoxycarbonylalkyle ayant 3 à 8 atomes de carbone, un groupe carboxyalkyle ayant 2 à 7 atomes de carbone, un groupe hydroxyalkyle ayant 2 à 5 atomes de carbone, un groupe hétérocyclique tel que défini dans la revendication 1, un groupe alcoxy ayant 1 à 5 atomes de carbone ou un groupé hydroxyle ;
A représente un groupe de formule $-CON(R^2)SO_2-$ où R^2 représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 12 atomes de carbone ; et
B représente une liaison simple, ou un groupe de formule -N(R5)- ou $-N(R^5)N(R^6)-$, où R^5 et R^6 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle ayant 1 à 12 atomes de carbone.

16. Composé selon la revendication 1 ou la revendication 2, dans lequel k est 4 ou 5.

17. Composé selon l'une quelconque des revendications 1, 2 et 16, dans lequel R^1 représente un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcoxycarbonylalkyle ayant 3 à 8 atomes de carbone, un groupe carboxyalkyle ayant 2 à 7 atomes de carbone, un groupe hydroxyalkyle ayant 2 à 5 atomes de carbone, un groupe hétérocyclique tel que défini dans la revendication 1 ou un groupe alcoxy ayant 1 à 5 atomes de carbone.

18. Composé selon l'une quelconque des revendications 1, 2, 16 et 17, dans lequel A représente un groupe de formule $-CONHSO_2-$ ou $-CONCH_3SO_2-$.

19. Composé selon l'une quelconque des revendications 1, 2 et 16 à 18, dans lequel B représente une liaison simple, ou un groupe de formule -NH-, $-NCH_3-$ ou $-NHNCH_3-$.

20. Composé selon la revendication 1 ou la revendication 2, dans lequel :

m et n sont tous deux 0 ;
k est 4 ou 5 ;
R^1 représente un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcoxycarbonylalkyle ayant 3 à 8 atomes de carbone, un groupe carboxyalkyle ayant 2 à 7 atomes de carbone, un groupe hydroxyalkyle ayant 2 à 5 atomes de carbone, un groupe hétérocyclique tel que défini dans la revendication 1 ou un groupe alcoxy ayant 1 à 5 atomes de carbone ;
A représente un groupe de formule $-CONHSO_2-$ ou $-CONCH_3SO_2-$; et
B représente une liaison simple ou un groupe de formule -NH-, $-NCH_3-$ ou $-NHNCH_3-$.

21. N-[5-(1,2-dithiolane-3-yl)pentanoyl]méthanesulfonamide et ses sels pharmaceutiquement acceptables.

22. Utilisation d'un composé selon l'une quelconque des revendications 1 à 21 pour la fabrication d'un médicament destiné à intensifier l'activité de glutathione-réductase chez un mammifère.

23. Utilisation d'un composé selon l'une quelconque des revendications 1 à 21 pour la fabrication d'un médicament destiné au traitement ou à la prévention de la cataracte chez un mammifère.

24. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 21 en mélange avec un diluant ou support pharmaceutiquement acceptable.